Synthetic studies on the cornexistins: synthesis of (±)-5-*epi*-hydroxycornexistin†‡

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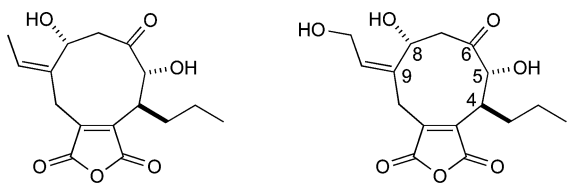
The synthesis of 5-*epi*-hydroxycornexistin (**44**), a diastereoisomer of the herbicidal natural product hydroxycornexistin (**2**) has been completed. Palladium mediated sp^2–sp^3 coupling of the stannane **25** and the chloride **31** and ring-closing metathesis of the resulting diene **32** has been used to construct the tricyclic lactone **34a**, which possesses the nine-membered carbocyclic core found in the natural product, in good yield. The synthesis of 5-*epi*-hydroxycornexistin (**44**) has established the feasibility of using a furan as precursor for the cyclic anhydride unit present in the natural product and has demonstrated the viability of other late-stage transformations that will be used to prepare hydroxycornexistin (**2**).

Introduction

Cornexistin (**1**) and hydroxycornexistin (**2**) are unusual members of the nonadride family of natural products (Fig. 1). Cornexistin was originally isolated from a culture of the fungus *Paecilomyces variotii* Bainier (strain SANK 21086) in 1987 by researchers at Sankyo Co. who were searching for new microbial products possessing herbicidal activity.[1] The structure of cornexistin was determined using NMR spectroscopy and by X-ray crystallography, but the absolute configuration was not established. Hydroxycornexistin was later obtained from the same strain of *P. variotii* by workers at DowElanco and its structure was determined by NMR analysis and a comparison of spectroscopic data to those of cornexistin.[2]



cornexistin (**1**) hydroxycornexistin (**2**)

Fig. 1 The cornexistins.

Both cornexistin (**1**) and hydroxycornexistin (**2**) display potent herbicidal activity against grasses and broadleaf weeds but are well tolerated by some crop plants such as maize (*Zea mays*);[3] hydroxycornexistin is a particularly potent herbicidal agent and exhibits good activity against many very aggressive varieties of broadleaf weed.[2,3] It has been suggested that the cornexisitins might exert their herbicidal activity by interfering with aspartate amino transferase isozymes,[3] but their precise mode of action is still unclear. As a consequence of their selective and potent herbicidal activity combined with their apparent novel mode of action, the cornexistins have significant potential as novel lead compounds in the search for new post-emergence weed control agents in crop production.[1–3]

The term "nonadride" was introduced by Barton and Sutherland[4] to refer to the bisanhydrides glauconic acid (**3**), glaucanic acid (**4**) and byssochlamic acid (**5**) because these natural products appeared to be biosynthesised from two C_9-units (Fig. 2). The term has since been extended to cover a range of related natural products that possess core structures in which a nine-membered carbocycle is fused to one or more maleic anhydride units.

The cornexistins are rather unusual members of the nonadride family because they possess just a single anhydride unit, while most of the others possess two (Fig. 2). The first of the nonadrides to be discovered—glauconic acid (**3**) and glaucanic acid (**4**)—were both isolated from the fungus *Penicillium glaucum* (now known as *Penicillium purpurogenum*) in 1931.[4] This was followed by the isolation of byssochlamic acid (**5**) from the fungus *Byssochlamys fulva* in 1933.[5] In each compound, the nine-membered carbocycle is substituted with simple alkyl side chains and in the case of glauconic acid there is an addition hydroxyl group. Subsequently, rubratoxins A (**6**) and B (**7**)—toxic metabolites of the fungus *Penicillium rubrum*—were isolated and found to possess more elaborate side chains appended to the nine-membered ring.[6] Interestingly, rubratoxin B does have some phytotoxic activity, but it is a much weaker herbicide than either of the cornexistins.[1–3] Finally, the nonadrides heveadride (**8**), homoheveadride (**9**),[7] dihydroepiheveadride (**10**)[8] and deoxoepiheveadride (**11**)[9] were isolated. Heveadride (**8**) has weak anti-fungal activity whereas dihydroepiheveadride has activity against a range of fungi,

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† Dedicated to Professor Andrew B. Holmes FRS on the occasion of his 65th birthday with much gratitude for his friendship and support over the past two decades.

‡ Electronic supplementary information (ESI) available: Experimental procedures for the preparation of compounds **21–25** and **27–32**. CCDC reference numbers 693628 (**34a**), 196700 (**34b**) and 693627 (**36**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b811245b

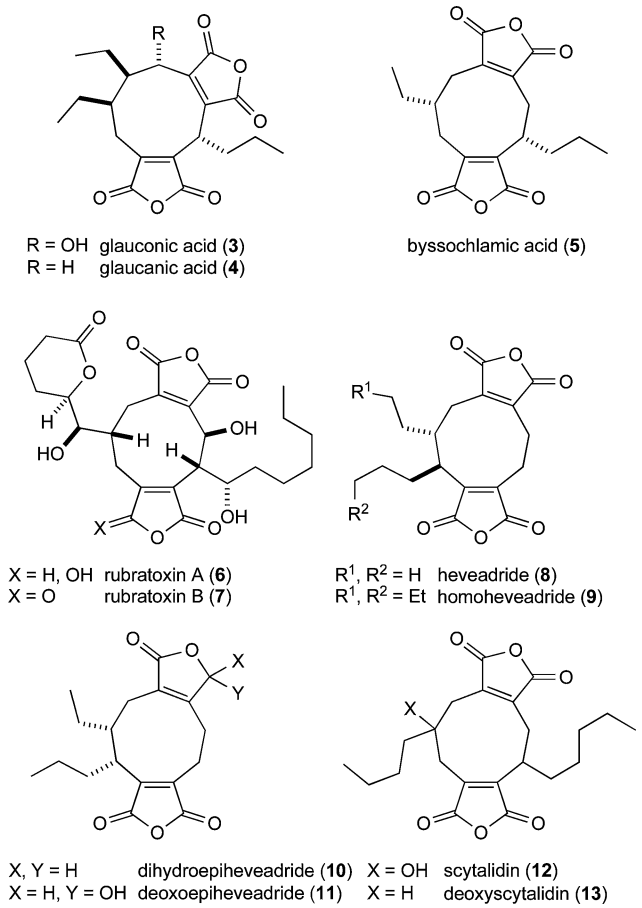


Fig. 2 Nonadride natural products related to the cornexistins.

including some human pathogens. Other nonadride natural products, such as scytalidin (**12**)[10] and deoxyscytalidin (**13**),[11] have also been shown to possess significant anti-fungal activity.[12]

The most structurally complex nonadrides to have been isolated to date are the fungal metabolites CP-225,917 (**14**) and CP-263,114 (**15**) (Fig. 3)—also known as phomoidrides A and B—which were discovered by workers at Pfizer in 1997.[13,14] In both

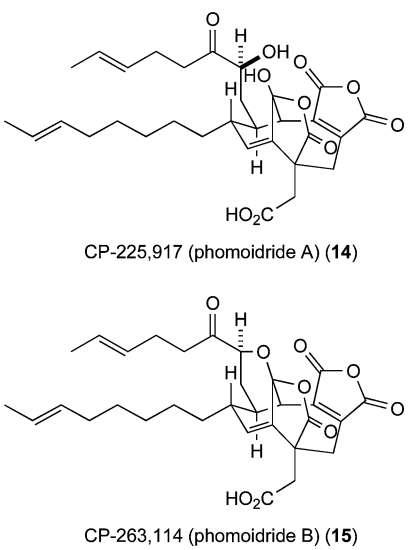
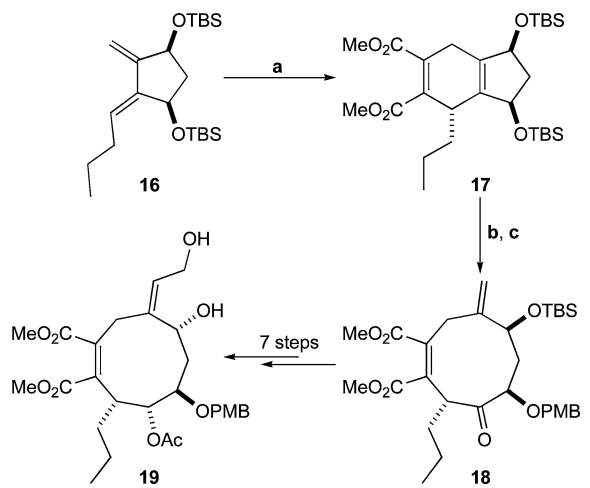


Fig. 3 The phomoidride natural products.

compounds the nine-membered carbocyclic core is embedded within a bicyclo[4.3.1]deca-1,6-diene framework. The compounds are the most widely studied of all the nonadrides and have aroused considerable interest in the pharmaceutical industry because they inhibit squalene synthase and Ras farnesyl transferase; inhibitors of these enzymes have been found to possess cholesterol-lowering and anti-cancer properties respectively.[14,15]

In spite of the significant potential they have as novel lead compounds in the search for new post-emergence weed control agents, the cornexistins have been the subject of relatively few synthetic studies and little has been published concerning their total synthesis. Aside from our own preliminary studies,[16] the only attempt to synthesise one of the cornexistins has been that recently reported by Taylor and co-workers.[17] In this work, the bicyclic compound **17**, prepared by intermolecular Diels–Alder cycloaddition of the diene **16** with dimethyl acetylenedicarboxylate, was subjected to ozonolytic ring opening and methylenation to give the cyclononenone **18** (Scheme 1). Further elaboration by inversion of configuration of one of the hydroxyl-bearing stereogenic centres and installation of the exocyclic trisubstituted alkene using a silicon-tethered diene ring-closing metathesis and Fleming–Tamao oxidation sequence gave the diol **19**. Elaboration of the diol **19** to give hydroxycornexistin was not reported by Taylor and co-workers.[17]

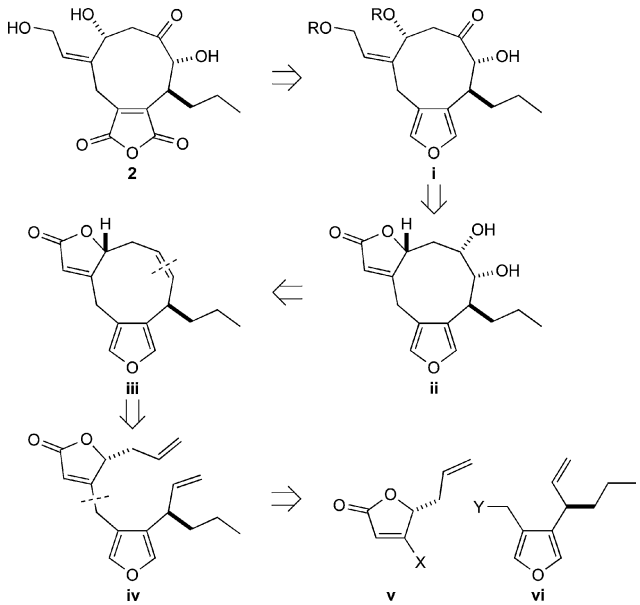


Scheme 1 Taylor's synthesis of an advanced intermediate for the synthesis of hydroxycornexistin. *Regents and conditions:* (a) $MeO_2CC{\equiv}CCO_2Me$, hydroquinone, PhMe, reflux [50%]; (b) O_3, CH_2Cl_2, −78 °C; (c) Tebbe reagent, THF, PhMe, −78 °C [45% over 2 steps].

Results and discussion

Our interest in cornexistin and hydroxycornexistin as synthetic targets was aroused by the synthetic challenges these compounds present coupled with their potent bioactivity. Both compounds possess a nine-membered carbocycle fused to a highly reactive cyclic anhydride, a combination of structural features that constitutes a significant obstacle to conventional methods of ring construction. In addition, the cornexistins present several potential problems concerning stereocontrol, with control of the exocyclic alkene configuration being especially challenging.

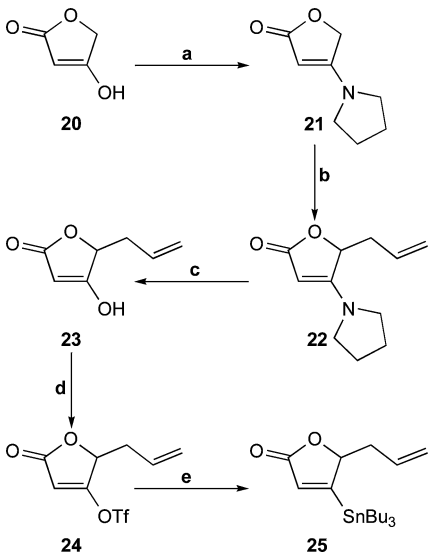
The retrosynthetic analysis of hydroxycornexistin that we devised begins with simple functional group interconversion (FGI) to mask the anhydride and give the furan **i** (Scheme 2). Connection of two of the hydroxyl groups in the form of a lactone and conversion of the ketone carbonyl group into a hydroxyl group then affords the diol **ii**. Conversion of the diol into an alkene then leads to the tricyclic lactone **iii** and disconnection of the ring through the alkene produces the diene **iv**. Disconnection of one of the bonds between the butenolide and the furan then delivers the simple lactone **v** and a 3,4-disubstituted furan **vi** bearing suitable substituents (X and Y) for a metal-mediated sp^2–sp^3 coupling reaction.



Scheme 2 Retrosynthetic analysis of hydroxycornexistin.

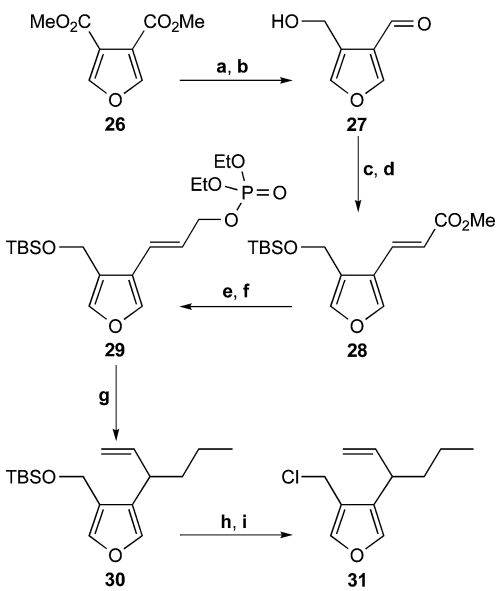
The key strategic transformation implied in our retrosynthetic analysis is construction of the nine-membered ring using a ring-closing metathesis (RCM) reaction. At the outset, we already had considerable experience in the preparation of medium-sized cyclic ethers using diene RCM reactions and other workers had used RCM to prepare other medium-ring carbocycles.[18,19] However, there were no literature examples involving direct construction of nine-membered carbocycles using RCM when we commenced our synthetic studies and so it was not clear whether a diene RCM reaction would deliver the nonadride core in good yield.

The first objective was the synthesis of the fragments (corresponding to synthons **v** and **vi** in Scheme 2) required for implementation of the synthetic plan suggested by our retrosynthetic analysis. In the case of synthon **v**, the corresponding stannane **25** was prepared as shown in Scheme 3. The readily available starting material tetronic acid (**20**) was first converted into the vinylogous carbamate **21** by condensation with pyrrolidine. Deprotonation of the compound **21** with *tert*-butyllithium and treatment of the resulting anion with allyl bromide then afforded the alkylated product **22**.[20] Acid-catalysed hydrolysis then delivered the tetronic acid derivative **23** and this was then converted into the triflate **24**. The stannane **25** required for the sp^2–sp^3 fragment coupling reaction was obtained in reasonable yield by the palladium-catalysed reaction of the triflate **24** with hexabutylditin.[21]



Scheme 3 Synthesis of the butenolide fragment **25**. *Reagents and conditions:* (a) pyrrolidine, heat [97%]; (b) *t*-BuLi, CH_2CHCH_2Br, THF, −78 °C → rt [76%]; (c) HCl aq., 60 °C [89%]; (d) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C [89%]; (e) $(Bu_3Sn)_2$, LiCl, $Pd(PPh_3)_4$, THF, reflux [54%].

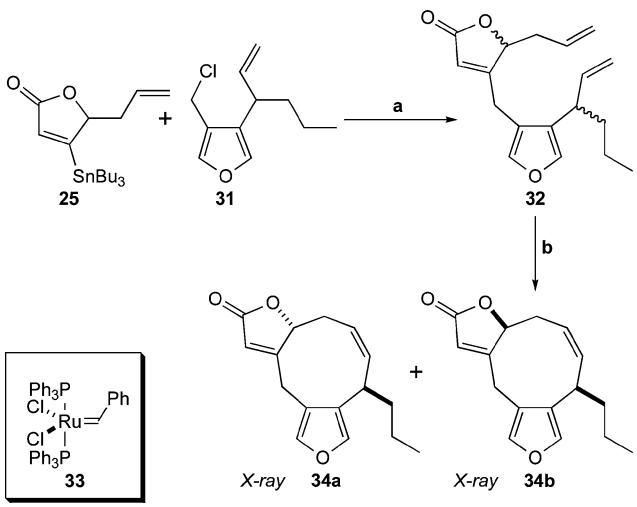
The synthesis of the second coupling partner commenced from commercially available furan dicarboxylate bisester **26** (Scheme 4). Reduction of the diester **26** with lithium aluminium hydride followed by selective mono-oxidation of the resulting diol with manganese dioxide afforded the aldehyde **27**.[22] Protection of the free hydroxyl group as a TBS ether followed by Wittig reaction of the aldehyde with methyl (triphenylphosphoranylidene)acetate



Scheme 4 Synthesis of the furan fragment **31**. *Reagents and conditions:* (a) $LiAlH_4$, THF, −78 °C → rt; (b) MnO_2, CH_2Cl_2, rt; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt [73% over 3 steps]; (d) $Ph_3P{=}CHCO_2Et$, THF, rt [89%]; (e) $LiAlH_4$, THF, −78 °C → rt [84%]; (f) $P(O)(OEt)_2Cl$, pyridine, DMAP, CH_2Cl_2, rt; (g) *n*-PrMgCl, CuCN (10 mol%), LiCl (30 mol%), THF, −78 °C [64% over 2 steps]; (h) TBAF, THF, rt [96%]; (i) $MeSO_2Cl$, LiCl, collidine, DMF, 0 °C, [77%].

delivered the α,β-unsaturated ester **28** in high yield. The ester was then reduced with lithium aluminium hydride and the resulting allylic alcohol was treated with diethyl chlorophosphate to give the allylic phosphate **29**. The propyl side chain was then installed by copper-catalysed S_N2' displacement of the allylic phosphate with *n*-propylmagnesium chloride following a procedure described by Yamamoto and co-workers, to give the alkene **30**.[23] Cleavage of the TBS ether and conversion of the resulting primary alcohol into the corresponding chloride *via* the mesylate, using a procedure described by Tanis for the synthesis of related chlorides,[24] afforded the chloride **31** which was to serve as the coupling partner.

The precursor required for the key diene RCM reaction was prepared by sp^2–sp^3 coupling of the vinylic stannane **25** and the chloride **31**.[25] The coupled product **32** was obtained in 87% yield (1 : 1 mixture of diastereoisomers) upon treatment of a mixture of the racemic stannane **25** and the racemic chloride **31** with $Pd_2(dba)_3$ and triphenylarsine in THF at reflux (Scheme 5). Ring closure was effected by subjecting the diastereomeric mixture of the dienes **32** to diene RCM using the ruthenium complex **33** in dichloromethane at reflux. The reaction was complete in 18 hours and the diastereomeric tricyclic products **34a** and **34b** were obtained as a separable mixture of diastereoisomers (2 : 3 ratio) in a combined yield of 77%.



Scheme 5 Construction of the nine-membered ring by fragment coupling and diene ring-closing metathesis. *Reagents and conditions:* (a) $Pd_2(dba)_3$ (3 mol%), $AsPh_3$ (8 mol%), THF, 60 °C [87%, 1 : 1]; (b) complex **33** (20 mol%), CH_2Cl_2, reflux [30% **34a**, 47% **34b**].

Both of the diastereoisomeric alkenes **34a** and **34b** were obtained as a crystalline solids. The compound **34b** crystallised readily to give crystals of suitable quality for X-ray analysis whereas the isomeric compound **34a** was obtained as an oil that subsequently crystallised to give a low-melting solid. X-ray analysis of both isomers revealed that the less polar compound was the tricyclic lactone **34a** possessing the relative stereochemistry required for the synthesis of the cornexistins (Fig. 4).‡

Dihydroxylation of the alkene **34a** using Upjohn conditions was sluggish,[26] but consistent yields of 50–55% could be obtained (~70% based on recovered alkene **34a**) (Scheme 6). The modest yields obtained from the dihydroxylation reaction suggest that decomposition of the alkene **34a** and/or the diol **35** occurs on

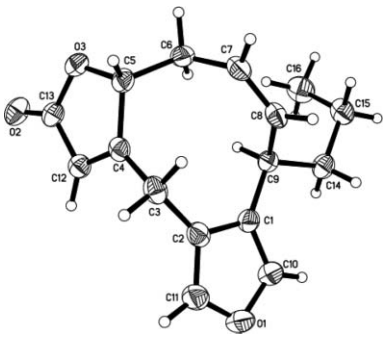
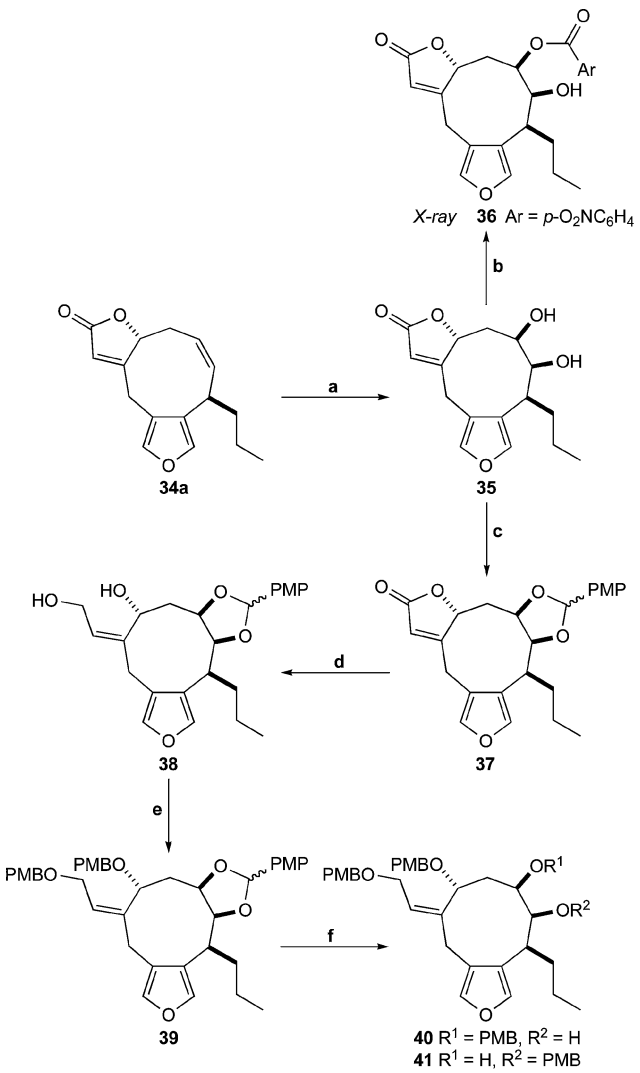


Fig. 4 X-Ray crystal structure of the RCM product **34a** (displacement ellipsoid plots drawn at 50% probability level).



Scheme 6 Conversion of RCM product **34a** into the advanced hydroxycornexistin precursors **40** and **41**. *Reagents and conditions:* (a) OsO_4 (10 mol%), NMO, Me_2CO, H_2O, rt [50–55% (55–70% based on recovered starting material)]; (b) *p*-$O_2NC_6H_4COCl$, DMAP, pyridine, CH_2Cl_2, 0 °C → rt [66%]; (c) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, 4 Å sieves, CH_2Cl_2, 0 °C → rt [93%, ~1 : 1]; (d) $LiAlH_4$, TMEDA, Et_2O, 0 °C; (e) NaH, $MeOC_6H_4CH_2Cl$, *n*-Bu_4NI, DMF, 0 °C → rt [49%, 2 steps]; (f) DiBAl-H, CH_2Cl_2, PhMe, –78 °C → rt [29% **40**, 33% **41** (81% based on recovered starting material)].

prolonged exposure to the reaction conditions. The stereochemical outcome of the dihydroxylation reaction was determined by X-ray analysis of the crystalline mono-*p*-nitrobenzoate **36** prepared by mono-esterification the diol **35** using *p*-nitrobenzoyl chloride (Scheme 6).‡ The relative configuration in the ester **36** meant that the dihydroxylation reaction had delivered the diol **35** with C-5 configuration that was opposite to that found in hydroxycornexistin (**2**) (Fig. 5).

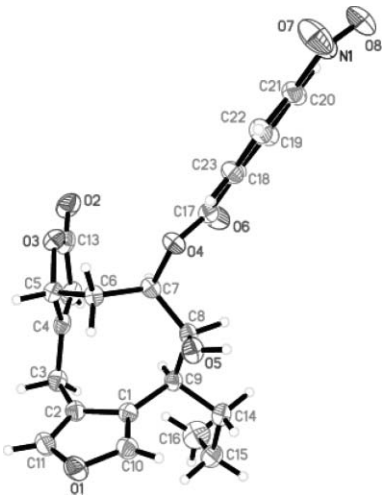


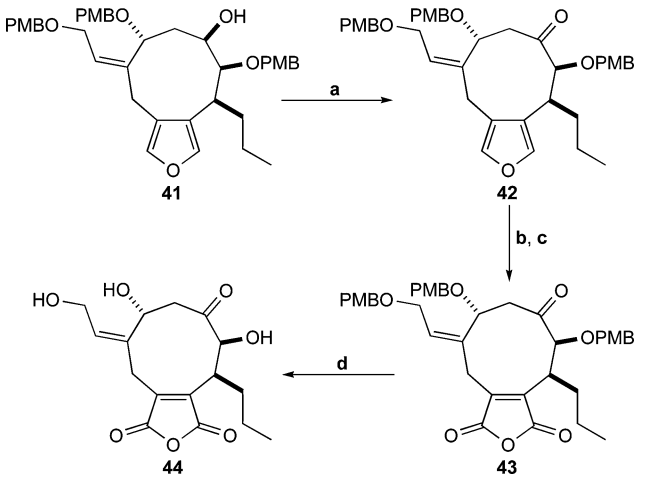
Fig. 5 X-Ray crystal structure of the *p*-nitrobenzoate **36** (displacement ellipsoid plots drawn at 50% probability level).

The X-ray crystal structure of the ester **34a** (Fig. 4) was remarkable because it clearly showed that dihydroxylation of the most accessible face of the alkene (*i.e.* that facing out from the ring) should deliver the required diastereomeric *syn* 1,2-diol product rather than the diol **35** (assuming free rotation of the propyl group). This finding illustrates the pitfalls of relying on X-ray crystal data to predict the reactive conformation of a conformationally mobile medium-ring system, such as the alkene **34a**, in solution.

Even though the dihydroxylation reaction had not delivered the diastereoisomer required for the total synthesis of hydroxycornexistin, further elaboration of the diol **35** was explored in order to complete the synthesis of 5-*epi*-hydroxycornexistin and thereby establish the viability of the steps late in the synthesis. It was also expected that it would be possible to complete the synthesis of hydroxycornexistin by inverting the stereochemistry at the hydroxyl-bearing stereogenic centre later in the synthesis.

The 1,2-diol **35** was converted into a diastereomeric mixture of the acetals **37** (1.3 : 1 ratio) by acid-catalysed transacetalation (Scheme 6). Lactone reduction using $LiAlH_4$ in the presence of TMEDA[27] and then double PMB protection of the resulting diols **38** afforded the acetals **39**. Reductive opening of this mixture of cyclic acetals with DiBAl-H produced the alcohols **40** and **41** (1 : 1.1 mixture) in 62% yield (81% based on recovered starting material).

The synthesis of (±)-5-*epi*-hydroxycornexistin (**44**) was completed as shown in Scheme 7. The alcohol **41** was converted into the ketone **42** in 80% yield by TPAP oxidation.[28] The final major transformation—conversion of the furan into the cyclic anhydride—was then performed by reaction of the furan **42** with singlet oxygen in the presence of Hünig's base followed by



Scheme 7 Completion of the synthesis of 5-*epi*-hydroxycornexistin. *Reagents and conditions:* (a) TPAP, 4 Å sieves, CH_2Cl_2, rt [80%]; (b) O_2, *hν*, rose Bengal, *i*-Pr_2NEt, −78 °C → rt; (c) TPAP, 4 Å sieves, CH_2Cl_2, rt; (d) DDQ, CH_2Cl_2, H_2O, rt [10% over 3 steps].

TPAP oxidation of the crude product.[29] The reaction with singlet oxygen delivered a complex mixture of products from which a 5-hydroxy-2(5*H*)-furanone could be isolated (39% yield) as the major component. The mixture of products resulting from singlet oxygen reaction was unstable, as was the cyclic anhydride **43**, and so removal of the PMB groups using DDQ was performed as quickly as possible after partial purification of the anhydride **43**. The resulting (±)-5-*epi*-hydroxycornexistin (**44**) was relatively unstable but could be purified by reverse phase HPLC giving an overall yield of 10% for the final three steps. The instability of the cyclic anhydride to silica gel and the extensive work-up required after deprotection account for the modest yield obtained for the three-step conversion of the bicyclic furan **42** into (±)-5-*epi*-hydroxycornexistin (**44**).

Comparison of the ^1H and ^{13}C NMR data for the natural product **2** with that of the synthetic C-5 diastereoisomer **44** revealed some interesting similarities and differences between the compounds (Table 1).[2b] Most of the ^{13}C NMR chemical shifts differed by less than 2 ppm and in some cases there was an excellent match even though the NMR samples did not have the same concentration and the NMR instruments differed. There was also some agreement with between the ^1H NMR data for the two compounds but in this case considerable differences in chemical shifts and coupling constants were obvious for some of the signals.

The completion of the synthesis of (±)-5-*epi*-hydroxycornexistin (**44**) demonstrated that the late-stage chemical transformations should be chemically viable for the total synthesis of hydroxycornexistin (**2**). Several attempts were then made to access the natural product by inversion of the C-5 stereocentre. In the first approach, Misunobu esterification with inversion of configuration was attempted using *p*-nitrobenzoic acid (Scheme 8).[30] Selective protection of the diol **35** by acetylation delivered a mixture of the diacetate **45** (20% yield) and the required monoacetate **46** (64% yield). Attempted Misunobu esterification of the free hydroxyl group of the monoacetate **46** with inversion of configuration using *p*-nitrobenzoic acid failed to deliver the required *p*-nitrobenzoate ester **47**. As an alternative, oxidation of the C-5 hydroxyl group followed by ketone reduction was explored. However, reduction

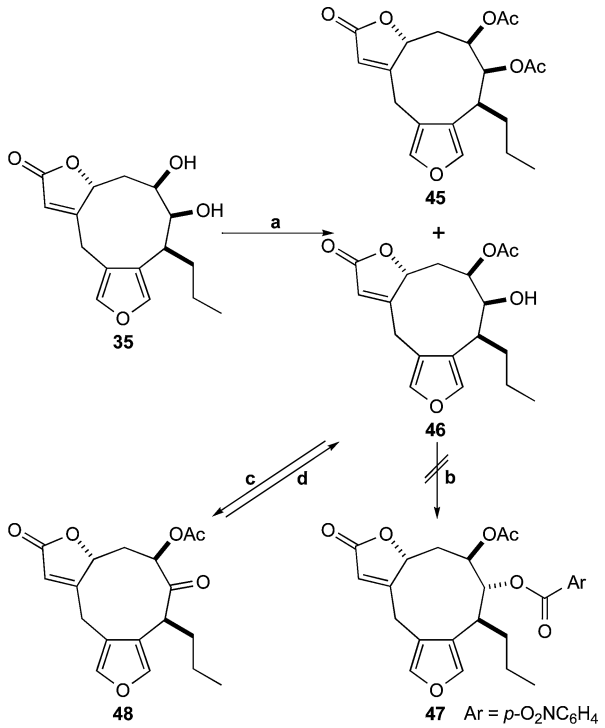
Table 1 Comparison of the ^{1}H and ^{13}C NMR data for natural hydroxycornexistin (**2**) and the synthetic (±)-5-*epi*-hydroxycornexistin (**44**)

^{1}H NMR data (CD_3CN)

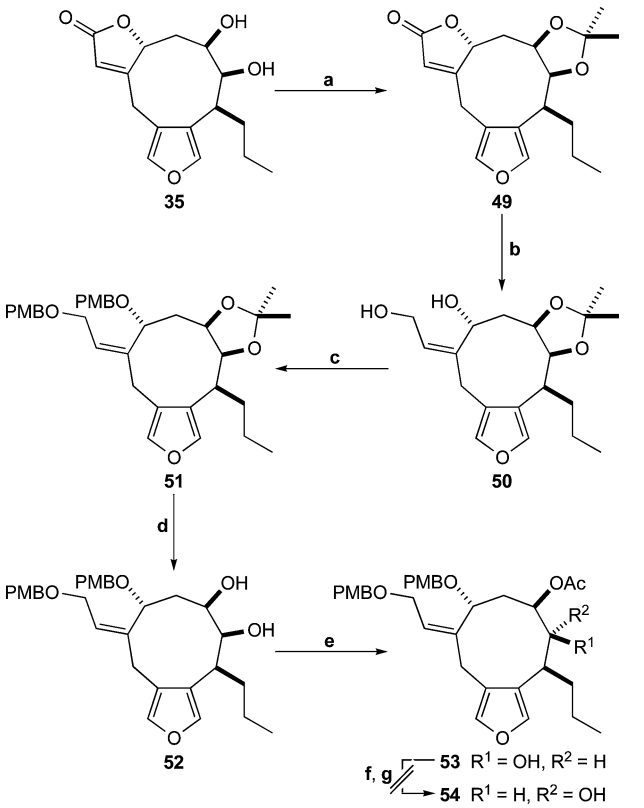
2 δ_H (300 MHz): 5.80 (1H, t, $J = 6.4$ Hz), 4.75 (1H, dd, $J = 8.8$, 4.9 Hz), 4.23–4.04 (2H, m), 3.81 (1H, d, $J = 9.5$ Hz), 3.44–3.34 (3H, m), 3.10 (1H, d), 2.58 (3H, br), 2.44 (1H, dd), 1.45–1.20 (2H, m), 0.89 (3H, t, $J = 7.3$ Hz) (2 × H missing due to overlap of solvent peak at ~2 ppm)
44 δ_H (500 MHz): 5.86 (1H, dd, $J = 6.5$, 5.9 Hz), 4.99 (1H, dd, $J = 10.3$, 6.2 Hz), 4.43–4.41 (1H, m), 4.16–4.14 (2H, m), 3.71 (1H, ddd, $J = 8.9$, 6.2, 2.5 Hz), 3.50 (1H, d, $J = 4.9$ Hz), 3.38 (1H, dd, $J = 16.5$, 10.3 Hz), 3.34 (1H, br s), 3.22 (1H, d, $J = 14.3$ Hz), 3.12 (1H, dd, $J = 14.3$, 1.1 Hz), 2.85 (1H, br s), 2.71 (1H, dd, $J = 16.5$, 6.2 Hz), 2.30–2.21 (1H, m), 1.92–1.86 (1H, m), 1.41–1.27 (2H, m), 0.95 (3H, t, $J = 7.4$ Hz)

^{13}C NMR data (CD_3CN)

2 δ_C (100 MHz): 212.5, 167.0, 166.3, 146.8, 142.6, 137.4, 135.6, 80.8, 68.3, 58.4, 44.7, 41.1, 30.6, 28.1, 21.7, 14.1
44 δ_C (125 MHz): 210.2, 166.8, 165.1, 147.4, 141.2, 137.6, 136.4, 79.4, 66.5, 58.4, 42.9, 41.0, 31.2, 25.2, 21.6, 14.3



Scheme 8 Attempted inversion of configuration at the C-5 stereocentre. *Reagents and conditions:* (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C → rt [20% **45**, 64% **46**]; (b) *p*-$O_2NC_6H_4CO_2H$, EtO_2CNNCO_2Et, PPh_3, THF, 0 °C → rt; (c) Dess–Martin periodinane, CH_2Cl_2, rt [95%]; (d) $NaBH_4$, THF, 0 °C [recovered **46**].



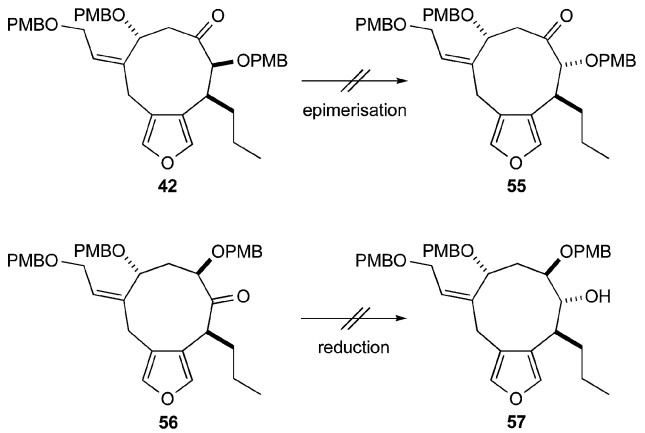
Scheme 9 Attempted inversion of configuration at the C-5 hydroxy-bearing stereogenic centre after opening of the lactone. *Reagents and conditions:* (a) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt [98%]; (b) DiBAl-H, CH_2Cl_2, PhMe, –78 °C then $LiAlH_4$, THF, –78 → 0 °C [74%]; (c) NaH, $MeOC_6H_4CH_2Cl$, *n*-Bu_4NI, DMF, 0 °C → rt [74%]; (d) *p*-TSA, MeOH, rt [54% (67% based on recovered starting material)]; (e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C → rt [65%]; (f) Dess–Martin periodinane, CH_2Cl_2, rt; (g) $NaBH_4$, THF, 0 °C [recovered **53**].

of the ketone **48** with $NaBH_4$ merely returned the original alcohol **46** (Scheme 8).

Further attempts to correct the configuration at the C-5 stereocentre were also made using intermediates lacking the lactone (Scheme 9). It was expected that lactone opening would result in a significant change in the conformation of the nine-membered ring and that this might lead to a reversal of facial selectivity during ketone reduction.

Prior to opening of the lactone, the diol **35** was converted into the acetonide **49** (Scheme 9). Initial attempts to reduce the lactone **49** with $LiAlH_4$ resulted in decomposition and the use of alternative reducing agents such as $LiBH_4$ and $NaBH_4$ was also unsuccessful. Transformation of the lactone **49** into the diol **50** was eventually accomplished in 74% yield by sequential one-pot reduction with DiBAl-H and then $LiAlH_4$. The diol **50** was protected as the bis-PMB ether **51** and removal of the acetonide under acidic conditions then afforded the diol **52**. Selective acetylation of the C-6 hydroxyl group and oxidation of the resulting alcohol **53** using the Dess–Martin periodinane provided the corresponding ketone. Reduction of this ketone with $NaBH_4$ did not deliver the required alcohol **54**; the only compound isolated was the original alcohol **53**.

Two further attempts were made to obtain hydroxycornexistin (Scheme 10). In the first case, epimerisation at the C-5 position of the ketone **42** was attempted using a variety of reagents,[31]



Scheme 10 Further attempts to correct the C-5 stereochemistry by epimerisation and oxidation/reduction in order to obtain hydroxycornexistin.

but unfortunately these reactions failed to deliver any of the required isomeric compound **55**. The second approach involved reduction of the ketone **56**, obtained by oxidation of the alcohol **40** (Scheme 6), using a variety of reducing agents.[32] Some of these reagents are known to give the thermodynamically rather than kinetically favoured product, but in all cases either the ketone **56** did not react or the alcohol **40** was obtained instead of the required alcohol **57**.

Conclusions

In summary, 5-*epi*-hydroxycornexistin (**44**) has been prepared from the tricyclic alkene **34a** in nine steps. The tricyclic alkene **34a** can be accessed by RCM of the diene produced by palladium-mediated coupling of the chloride **31** and the stannane **25** and these fragments can be prepared from readily available starting materials in nine and five steps respectively.

Our synthesis of 5-*epi*-hydroxycornexistin (**44**) has demonstrated the feasibility of the late-stage transformations that will be used to prepare hydroxycornexistin (**2**). Preliminary attempts to access the natural product by inversion of configuration at the C-5 stereogenic centre have not been successful, but work is continuing in an effort to synthesise both cornexistins using the strategy described herein.

Experimental

(4*R**,5*Z*,7a*R**)-4-Propyl-7,7a-dihydro-4*H*,11*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-9-one 34a and (4*R**,5*Z*,7a*S**)-4-propyl-7,7a-dihydro-4*H*,11*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-9-one 34b

The ruthenium catalyst **33** (654 mg, 0.798 mmol) was added to a stirred solution of a mixture (1 : 1) of the diastereomeric dienes **32** (1.14 g, 4.01 mmol) in dichloromethane (1.0 L) at room temperature. The resulting red solution was heated at reflux for 18 h and then cooled to room temperature. The brown solution was stirred under an air atmosphere for 1 h then concentrated to afford the crude mixture of alkenes **34a** and **34b** as a brown oil. Purification by flash column chromatography on silica gel (petroleum ether–diethyl ether, 7 : 3 → 1 : 1) yielded the alkenes **34a** (309 mg, 30%) and **34b** (484 mg, 47%) as colourless solids. Recrystallisation of the alkene **34a** from hexane and ethyl acetate and recrystallisation of the alkene **34b** from petroleum ether and dichloromethane gave crystals suitable for X-ray crystallography.

34a. Mp 77–79 °C (Found: C, 74.10; H, 6.95; $C_{16}H_{18}O_3$ requires: C, 74.40; H, 7.02%); R_f: = 0.18 (petroleum ether–diethyl ether, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2930, 2873, 1796, 1748, 1634, 901, 871; δ_H (500 MHz, $CDCl_3$) 7.34 (1H, s, Fur-*H*), 7.21 (1H, dd, J = 1.6, 1.3 Hz, Fur-*H*), 5.87 (1H, s, COC*H*=C), 5.78 (1H, ddd, J = 10.2, 10.0, 6.8 Hz, CH_2CH=CH), 5.42 (1H, dd, J = 10.2, 10.2 Hz, CH=C*H*CH), 4.92 (1H, dd, J = 10.2, 5.5 Hz, CH=CC*H*O), 3.55 (1H, d, J = 15.4 Hz, CH_2C=CH), 3.50 (1H, d, J = 15.4 Hz, CH_2C=CH), 3.41 (1H, ddd, J = 10.2, 9.6, 4.0 Hz, C*H*CH=CH), 2.88 (1H, ddd, J = 13.0, 6.8, 5.5 Hz, CH_2CH=CH), 2.54 (1H, ddd, J = 13.0, 10.2, 10.0 Hz, CH_2CH=CH), 1.86–1.78 (1H, m, CHCH_2CH$_2$), 1.59–1.50 (1H, m, CHCH_2CH$_2$), 1.49–1.38 (1H, m, CH_2CH_3), 1.34–1.23 (1H, m, CH_2CH_3), 0.93 (3H, t, J = 7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 172.8 (C), 172.6 (C), 140.8 (CH), 139.5 (CH), 136.8 (CH), 125.3 (C), 120.7 (C), 122.1 (CH), 119.0 (CH), 81.6 (CH), 34.4 (CH_2), 33.5 (CH), 33.3 (CH_2), 23.1 (CH_2), 20.3 (CH_2), 14.1 (CH_3); m/z (EI) 258.1248 [M]$^+$, $C_{16}H_{18}O_3$ requires 258.1256.

34b. Mp 92–95 °C (Found: C, 74.17; H, 7.05; $C_{16}H_{18}O_3$ requires C, 74.40; H, 7.02%); R_f: = 0.10 (petroleum ether–diethyl ether, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2932, 2873, 1748, 1641, 975, 938, 910, 885; δ_H (500 MHz, $CDCl_3$) 7.38 (1H, d, J = 1.1 Hz, Fur-*H*), 7.17 (1H, s, Fur-*H*), 5.74 (1H, s, COC*H*=C), 5.29 (1H, ddd, J = 10.8, 10.6, 5.3 Hz, CH_2CH=CH), 5.25 (1H, dd, J = 10.8, 9.7 Hz, CH=C*H*CH), 5.24 (1H, dd, J = 4.4, 2.1 Hz, CH=CC*H*O), 3.57 (1H, dd, J = 15.3, 1.4 Hz, CH_2C=CH), 3.39 (1H, ddd, J = 9.7, 9.3, 5.5 Hz, C*H*CH=CH), 3.17 (1H, d, J = 15.3 Hz, CH_2C=CH), 3.14–3.05 (1H, m, CH_2CH=CH), 2.76 (1H, ddd, J = 14.4, 5.3, 4.4 Hz, CH_2CH=CH), 1.70–1.63 (2H, m, CHCH_2CH$_2$), 1.43–1.39 (1H, m, CH_2CH_3), 1.33–1.27 (1H, m, CH_2CH_3), 0.93 (3H, t, J = 7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 172.8 (C), 170.7 (C), 140.0 (CH), 139.2 (CH), 139.0 (CH), 128.1 (C), 121.3 (C), 119.9 (CH), 119.8 (CH), 84.5 (CH), 35.2 (CH_2), 32.8 (CH), 28.0 (CH_2), 21.1 (CH_2), 20.8 (CH_2), 13.9 (CH_3); m/z (EI) 258.1256 [M]$^+$, $C_{16}H_{18}O_3$ requires 258.1256.

X-Ray crystal structure data for alkene 34a. $C_{16}H_{18}O_3$, M = 258.30, monoclinic, a = 10.3476(7), b = 12.7195(9), c = 11.1244(8) Å, β = 114.035(2)°, U = 1337.21(16) Å^3, T = 150(2) K, space group $P2_1/n$, Z = 4, D_c = 1.283 g cm^{-3}, μ(Mo-Kα) = 0.088 mm^{-1}, 12219 reflections collected, 3087 unique (R_{int} = 0.096). Final R_1 [2629 $F > 4\sigma(F)$] = 0.0436, wR_2 [all F^2] = 0.122. CCDC number 693628.‡

X-Ray crystal structure data for alkene 34b. $C_{16}H_{18}O_3$, M = 258.30, monoclinic, a = 16.9137(13), b = 8.9021(7), c = 9.1712(7) Å, β = 102.642(1)°, U = 1347.4(2) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, D_c = 1.273 g cm^{-3}, μ(Mo-Kα) = 0.087 mm^{-1}, 11825 reflections collected, 3390 unique (R_{int} = 0.066). Final R_1 [2766 $F > 4\sigma(F)$] = 0.0395, wR_2 [all F^2]= 0.120. CCDC number 196700.‡

(4*S,5*S**,6*R**,7a*R**)-5,6-Dihydroxy-4-propyl-5,6,7,7a-tetrahydro-4*H*,11*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-9-one 35**

The alkene **34a** (218 mg, 0.844 mmol) was dissolved in a mixture of acetone (9 mL) and water (1 mL). *N*-Methylmorphine-*N*-oxide (119 mg, 1.01 mmol) and osmium tetroxide (0.52 mL of a 4 mol% solution in water, 0.084 mmol) were then added and the mixture was stirred for 12 h at room temperature. The dihydroxylation reaction was then quenched by the addition of a saturated aqueous solution of sodium metabisulfite (15 mL) and the resulting mixture stirred at room temperature for 1 h. The mixture was diluted with water (15 mL) and ethyl acetate (30 mL) and the aqueous phase was separated and washed with further ethyl acetate (2 × 20 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 1 : 1) to give the diol **35** as a colourless oil which solidified on standing (123 mg, 50%): mp 75–78 °C; R_f: = 0.16 (petroleum ether–ethyl acetate, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3604, 2959, 2991, 1754, 1630, 1602, 979, 909, 872; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, J = 1.5 Hz, Fur-*H*), 7.30 (1H, dd, J = 1.5, 1.4 Hz, Fur-*H*), 6.11 (1H, s, COC*H*=C), 5.01 (1H, br s, CH=CC*H*O), 3.87 (1H, br s, CHC*H*OH), 3.81 (1H, d, J = 18.4 Hz, CH_2C=CH), 3.68 (1H, dd, J = 18.4, 1.4 Hz, CH_2C=CH), 3.23 (1H, br d, J = 5.3 Hz, CH$_2$C*H*OH), 2.91 (2H, br s, 2 × O*H*), 2.33 (1H, dd, J = 9.5, 6.0 Hz, C*H*CH$_2$CH$_2$), 1.91 (1H, ddd, J = 16.5, 5.3, 2.7 Hz, CHCH_2CH), 1.80–1.70 (2H, m, CHCH_2CH, CHCH_2CH$_2$), 1.68–1.61 (1H, m, CHCH_2CH$_2$), 1.29–1.23 (2H, m, CH_2CH$_3$), 0.85 (3H, t, J = 7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 172.8 (C), 169.5 (C), 142.7 (CH), 139.8 (CH), 122.8 (C), 119.4 (CH), 118.6 (C), 82.8 (CH), 74.7 (CH), 68.1 (CH), 37.8 (CH$_2$), 36.4 (CH), 33.4 (CH$_2$), 24.2 (CH$_2$), 20.6 (CH$_2$), 13.9 (CH$_3$); *m*/*z* (EI) 292.1316 [M]$^+$, $C_{16}H_{20}O_5$ requires 292.1311.

4-Nitrobenzoic acid (4*S,5*S**,6*R**,7a*R**)-5-hydroxy-9-oxo-4-propyl-5,6,7,7a,9,11-hexahydro-4*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-6-yl ester 36**

Pyridine (47 μL, 0.58 mmol), DMAP (1.5 mg, 0.012 mmol) and *p*-nitrobenzoyl chloride (21.5 mg, 0.116 mmol) were added to a stirred solution of the diol **35** (34.0 mg, 0.116 mmol) in dichloromethane (1.5 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Additional *p*-nitrobenzoyl chloride (64.5 mg, 0.348 mmol) was added and stirring was continued for a further 1 h. The reaction mixture was poured into water (5 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were washed with a saturated aqueous solution of copper sulfate (3 × 5 mL) and brine (5 mL) then dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the crude product as a pale yellow solid. Purification by flash column chromatography on silica gel (0 → 10% ethyl acetate in dichloromethane) yielded the ester **36** as a colourless solid (34.1 mg, 66%). Recrystallisation from dichloromethane and hexane gave colourless crystals suitable for X-ray crystallography: mp 172–175 °C (Found: C, 62.51; H, 5.17; N, 3.20; $C_{23}H_{23}NO_8$ requires: C, 62.58; H, 5.25; N, 3.17%); R_f: = 0.51 (ethyl acetate–petroleum ether, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3622, 2959, 2932, 1759, 1724, 1631, 1608, 970, 909, 872; δ_H (400 MHz, $CDCl_3$) 8.27 (2H, ddd, J = 9.0, 2.1, 2.1 Hz, 2 × Ar-*H*), 8.18 (2H, ddd, J = 9.0, 2.1, 2.1 Hz, 2 × Ar-*H*), 7.39 (1H, dd, J = 1.6, 1.1 Hz, Fur-*H*), 7.37 (1H, d, J = 1.6 Hz, Fur-*H*), 6.24 (1H, s, COC*H*=C), 5.03 (1H, br s, CH=CC*H*O), 4.84 (1H, ddd, J = 4.2, 2.5, 2.4 Hz, C*H*O$_2$CAr), 4.04 (1H, br s, C*H*OH), 3.90 (1H, dd, J = 18.4, 1.1 Hz, CH_2C=CH), 3.79 (1H, br d, J = 18.4 Hz, CH_2C=CH), 2.56 (1H, dd, J = 9.3, 6.2 Hz, C*H*CH$_2$CH$_2$), 2.12–1.99 (3H, m, CHCH_2CH, O*H*), 1.81–1.60 (2H, m, CHCH_2CH$_2$), 1.36–1.24 (2H, m, CH_2CH$_3$), 0.88 (3H, t, J = 7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 171.6 (C), 167.8 (C), 163.4 (C), 150.7 (C), 142.6 (CH), 140.7 (CH), 135.4 (C), 131.0 (CH), 123.6 (CH), 122.4 (C), 120.4 (CH), 118.7 (C), 81.6 (CH), 72.6 (CH), 72.6 (CH), 37.1 (CH$_2$), 37.0 (CH), 30.5 (CH$_2$), 23.9 (CH$_2$), 20.5 (CH$_2$), 13.8 (CH$_3$); *m*/*z* (EI) 464.1303 [M + Na]$^+$, $C_{23}H_{23}NaNO_8$ requires 464.1321.

X-Ray crystal structure data for alkene 36. $C_{23}H_{23}NO_8$, M = 441.42, monoclinic, a = 7.2351(7), b = 25.532(2), c = 12.0626(12) Å, β = 104.539(2)°, U = 2156.9(3) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, D_c = 1.359 g cm^{-3}, μ(Mo-Kα) = 0.104 mm^{-1}, 18983 reflections collected, 4848 unique (R_{int} = 0.067). C Final R_1 [3821 $F > 4\sigma(F)$] = 0.0406, wR_2 [all F^2]= 0.121. CDCC number 693627.‡

(4*S,5*S**,6*R**,7a*R**)-5,6-[(4-Methoxyphenyl)methylenedioxy]-4-propyl-5,6,7,7a-tetrahydro-4*H*,11*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononene-9-one 37**

The diol **35** (127 mg, 0.434 mmol) was dissolved in dichloromethane (4.5 mL) and powdered 3 Å molecular sieves (20 mg) was added followed by camphorsulfonic acid (20 mg, 0.086 mmol). The mixture was cooled to 0 °C and *p*-anisaldehyde dimethyl acetal (0.11 mL, 0.65 mmol) was added. The mixture was stirred at 0 °C for 15 min and then warmed to room temperature and allowed to stir at this temperature for a further 2 h. The reaction mixture was diluted with dichloromethane (5 mL), filtered and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 4 : 1 then 1 : 1) to give an inseparable mixture (1.3 : 1) of the acetals **37** (166 mg, 93%) as a colourless solid: mp 58–60 °C (Found: C, 69.84; H, 6.28; $C_{24}H_{26}O_6$ requires C, 70.23; H, 6.38%); R_f: = 0.28 (petroleum ether–ethyl acetate, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2933, 1751, 1614, 964; δ_H (400 MHz, $CDCl_3$) *major isomer* 7.38 (1H, s, Fur-*H*), 7.35–7.25 (3H, m, Fur-*H*, 2 × Ar-*H*), 6.91–6.86 (2H, m, 2 × Ar-H), 6.09 (1H, s, COC*H*=C), 5.68 (1H, s, OC*H*O), 4.93 (1H, d, J = 4.5 Hz, CH=CC*H*O), 4.13–4.02 (2H, m, C*H*OCHArOC*H*), 3.92 (1H, d, J = 17.5 Hz, CH_2C=CH), 3.81 (3H, s, OCH_3), 3.68–3.64 (1H, m, CH_2C=CH), 2.77 (1H, ddd, J = 10.1, 5.2, 1.4 Hz, C*H*CH$_2$CH$_2$), 2.13–2.02 (1H, m, CHCH_2CH), 1.95–1.60 (3H, m, CHCH_2CH, CHCH_2CH$_2$), 1.36–1.20 (2H, m, CH_2CH$_3$), 0.89 (3H, t, J = 7.3 Hz, CH$_3$); *minor isomer* 7.41 (1H, s, Fur-*H*), 7.35–7.25 (3H, m, Fur-*H*, 2 × Ar-*H*), 6.91–6.86 (2H, m, 2 × Ar-*H*), 6.09 (1H, s, COC*H*=C), 5.84 (1H, s, OC*H*O), 4.99 (1H, d, J = 4.9 Hz, CH=CC*H*O), 4.13–4.02 (2H, m, C*H*OCHArOC*H*), 3.89 (1H, d, J = 16.8 Hz, CH_2C=CH), 3.81 (3H, s, OCH_3), 3.68–3.64 (1H, m, CH_2C=CH), 2.65 (1H, dd, J = 10.2, 5.1 Hz, C*H*CH$_2$CH$_2$), 2.13–2.02 (1H, m, CHCH_2CH), 1.95–1.60 (3H, m, CHCH_2CH, CHCH_2CH$_2$), 1.36–1.20 (2H, m, CH_2CH$_3$), 0.86 (3H, t, J = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) *major isomer* 172.1 (C), 169.5 (C), 160.5 (C), 142.6 (CH), 139.1 (CH), 131.6 (C), 128.3 (CH), 123.7 (C), 123.6 (C), 118.6 (CH),

113.8 (CH), 102.6 (CH), 82.0 (CH), 80.3 (CH), 73.1 (CH), 55.4 (CH_3), 38.8 (CH_2), 34.3 (CH_2), 33.0 (CH), 24.9 (CH_2), 20.7 (CH_2), 13.8 (CH_3); *minor isomer* 172.1 (C), 169.5 (C), 160.2 (C), 142.5 (CH), 139.1 (CH), 130.1 (C), 127.6 (CH), 123.7 (C), 123.6 (C), 118.9 (CH), 113.8 (CH), 102.0 (CH), 81.7 (CH), 78.2 (CH), 72.1 (CH), 55.4 (CH_3), 38.8 (CH_2), 33.3 (CH), 32.6 (CH_2), 24.8 (CH_2), 20.7 (CH_2), 13.8 (CH_3); *m/z* (EI) 411.1788 $[M + H]^+$, $C_{24}H_{27}O_6$ requires 411.1802.

(3a*R,5*R**,6*Z*,11*S**,11a*S**)-5-[(4-Methoxybenzyl)oxy]-6-{2-[(4-methoxybenzyl)oxy]ethylidene}-2-(4-methoxyphenyl)-11-propyl-4,5,6,7,11,11a-hexahydro-3a*H*-furo[3′,4′:4,5]cyclonona[1,2-*d*][1,3]dioxole 39**

Lithium aluminium hydride (42.3 mg, 1.11 mmol) was added to a stirred solution of TMEDA (135 μL, 0.900 mmol) in diethyl ether (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 10 min, cooled to 0 °C and then stirred for a further 20 min. To this suspension was added the lactone **37** (183 mg, 0.446 mmol) and stirring was continued for 1 h. The reaction was quenched by careful addition of water (0.5 mL) and the mixture was warmed to room temperature. The mixture was diluted with diethyl ether (5 mL) and the organic layer was separated, dried ($MgSO_4$) and concentrated to give the crude diol **38** as a colourless solid.

The diol was dissolved in dry DMF (5 mL) at 0 °C under argon. Tetra-*n*-butylammonium iodide (16.3 mg, 0.0441 mmol) was added along with *p*-methoxybenzyl chloride (141 μL, 1.12 mmol) and sodium hydride (89.2 mg of a 60% dispersion in mineral oil, 2.23 mmol). The reaction mixture was stirred at 0 °C for 2 h then quenched by addition of water (5 mL). The mixture was diluted with diethyl ether (10 mL) and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic layers were combined, washed with a saturated aqueous solution of copper sulfate (3 × 10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated to afford the crude product as a pale yellow oil. Purification by flash column chromatography on silica gel (0 → 30% ethyl acetate in hexane with 1% triethylamine) yielded a diastereomeric mixture (~2 : 1) of the acetals **39** (142 mg, 49% over 2 steps) as a colourless oil: R_f: = 0.28 (petroleum ether–ethyl acetate, 4 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2934, 2862, 2838, 1682, 1614, 1587, 1508; δ_H (500 MHz, C_6D_6, 343 K) *major isomer* 7.41 (2H, d, *J* = 8.7 Hz, 2 × Ar-*H*), 7.37 (1H, d, *J* = 1.6 Hz, Fur-*H*), 7.25–7.17 (4H, m, 4 × Ar-*H*), 7.03 (1H, dd, *J* = 1.3, 1.1 Hz, Fur-*H*), 6.84–6.75 (6H, m, 6 × Ar-*H*), 5.81–5.78 (1H, m, C=C*H*CH_2O), 5.78 (1H, s, OC*H*O), 4.66 (1H, ddd, *J* = 11.0, 6.7, 2.5 Hz, CH_2C*H*OCHArO), 4.38–4.12 (7H, m, 2 × CH_2Ar, C*H*OCH_2Ar, OCHArOC*H*CH, CH_2OCH_2Ar), 4.03 (1H, dd, *J* = 12.7, 5.4 Hz, CH_2OCH_2Ar), 3.72 (1H, ddd, *J* = 9.6, 6.0, 1.6 Hz, C*H*CH_2CH_2), 3.39–3.36 (1H, m, CH_2C=CH), 3.39 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.07 (1H, d, *J* = 14.5 Hz, CH_2C=CH), 2.18–1.98 (2H, m, CHCH_2CH), 1.90–1.65 (2H, m, CHCH_2CH_2), 1.36–1.22 (2H, m, CH_2CH_3), 0.83 (3H, t, *J* = 7.4 Hz, CH_3); *minor isomer* 7.49 (2H, d, *J* = 8.4 Hz, 2 × Ar-*H*), 7.43 (1H, d, *J* = 1.5 Hz, Fur-*H*), 7.25–7.17 (4H, m, 4 × Ar-*H*), 7.01 (1H, dd, *J* = 1.4, 1.3 Hz, Fur-*H*), 6.84–6.75 (6H, m, 6 × Ar-*H*), 5.99 (1H, s, OC*H*O), 5.84–5.81 (1H, m, C=C*H*CH_2O), 4.83–4.79 (1H, m, CH_2C*H*OCHArO), 4.38–4.12 (8H, m, 2 × CH_2Ar, C*H*OCH_2Ar, OCHArOC*H*CH, CH_2OCH_2Ar), 3.54–3.52 (1H, m, C*H*CH_2CH_2), 3.39–3.36 (1H, m, CH_2C=CH), 3.38 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.09 (1H, d, *J* = 14.7 Hz, CH_2C=CH), 2.18–1.98 (2H, m, CHCH_2CH), 1.90–1.65 (2H, m, CHCH_2CH_2), 1.36–1.22 (2H, m, CH_2CH_3), 0.80 (3H, t, *J* = 7.4 Hz, CH_3); δ_C (125 MHz, C_6D_6, 343 K) *major isomer* 161.1 (C), 160.1 (C), 160.1 (C), 142.7 (CH), 141.8 (C), 138.8 (CH), 131.7 (C), 131.5 (C), 131.1 (C), 129.6 (CH), 129.5 (CH), 128.9 (CH), 127.5 (CH), 125.5 (C), 124.5 (C), 114.5 (CH), 114.4 (CH), 114.2 (CH), 102.8 (CH), 81.9 (CH), 76.2 (CH), 75.1 (CH), 72.6 (CH_2), 70.9 (CH_2), 66.6 (CH_2), 55.0 (CH_3), 55.0 (CH_3), 55.0 (CH_3), 39.7 (CH_2), 36.1 (CH_2), 34.0 (CH), 31.0 (CH_2), 21.1 (CH_2), 14.0 (CH_3); *minor isomer* 160.8 (C), 160.1 (C), 160.1 (C), 142.6 (CH), 140.9 (C), 138.8 (CH), 133.5 (C), 131.0 (C), 128.4 (CH), 128.1 (CH), 127.9 (CH), 125.5 (C), 124.0 (C), 114.5 (CH), 114.4 (CH), 114.2 (CH), 102.3 (CH), 80.2 (CH), 76.7 (CH), 75.8 (CH), 72.7 (CH_2), 70.9 (CH_2), 66.9 (CH_2), 55.0 (CH_3), 39.6 (CH_2), 35.3 (CH_2), 34.3 (CH), 32.0 (CH_2), 21.1 (CH_2), 14.0 (CH_3); *m/z* (EI) 654.3188 $[M]^+$, $C_{40}H_{46}O_8$ requires 654.3193.

(4*S,5*S**,6*R**,8*R**,9*Z*)-6,8-Bis[(4-methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]ethylidene}-4-propyl-5,6,7,8,9,10-hexahydro-4*H*-cyclonona[*c*]furan-5-ol 40 and (4*S**,5*S**,6*R**,8*R**,9*Z*)-5,8-bis[(4-methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]-ethylidene}-4-propyl-5,6,7,8,9,10-hexahydro-4*H*-cyclonona[*c*]furan-6-ol 41**

A solution of diisobutylaluminium hydride (260 μL of a 1.0 M solution in toluene, 0.260 mmol) was added to a stirred solution of the acetals **39** (85.3 mg, 0.130 mmol) in dichloromethane at −78 °C under argon. The reaction mixture was stirred at −78 °C for 2 h then three further portions of a solution of diisobutylaluminium hydride (260 μL of a 1.0 M solution in toluene, 0.260 mmol) were added at 2 h intervals. The reaction mixture was then quenched with methanol (1 mL), warmed to room temperature, then poured into a saturated aqueous solution of potassium sodium tartrate (10 mL). The aqueous phase was extracted with dichloromethane (5 × 10 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to afford the crude product mixture as a pale yellow oil. Purification by flash column chromatography on silica gel (30 → 40% diethyl ether in hexane) yielded the alcohols **40** (25.0 mg, 29%) and **41** (28.0 mg, 33%) and the original mixture of acetals **39** (20.1 mg, 24%) as colourless oils.

40. R_f: = 0.40 (60% diethyl ether in petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3569, 2957, 2935, 2863, 2838, 1613, 1586, 870; δ_H (400 MHz, $CDCl_3$) 7.26–7.13 (8H, m, 6 × Ar-*H*, 2 × Fur-*H*), 6.89–6.79 (6H, m, 6 × Ar-*H*), 5.80 (1H, dd, *J* = 6.1, 4.4 Hz, C=C*H*CH_2O), 4.53 (1H, d, *J* = 11.9 Hz, OCH_2Ar), 4.44 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.34 (1H, d, *J* = 11.9 Hz, OCH_2Ar), 4.32 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.29–4.25 (1H, m, CH_2OCH_2Ar), 4.25 (2H, s, CH_2OCH_2Ar), 4.09 (1H, dd, *J* = 13.3, 6.1 Hz, OCH_2Ar), 3.95–3.92 (2H, m, C*H*OH, CH=CC*H*O), 3.82 (3H, s, OCH_3), 3.77 (6H, 2 × OCH_3), 3.54 (1H, d, *J* = 5.4 Hz, CHC*H*OCH_2Ar), 3.36 (1H, d, *J* = 15.5 Hz, CH_2C=CH), 3.24 (1H, d, *J* = 15.5 Hz, CH_2C=CH), 2.83 (1H, dd, *J* = 9.7, 5.9 Hz, C*H*CH_2CH_2), 2.17 (1H, d, *J* = 4.0 Hz, O*H*), 1.91–1.57 (4H, m, CHCH_2CH, CHCH_2CH_2), 1.33–1.25 (2H, m, CH_2CH_3), 0.87 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 159.2 (C), 159.1 (C), 159.0 (C), 142.0 (CH), 139.1 (CH), 137.4 (C), 130.9 (C), 130.5 (C),

130.5 (C), 129.4 (CH), 129.1 (CH), 128.8 (CH), 123.5 (C), 122.1 (C), 113.8 (CH), 113.8 (CH), 78.2 (CH), 77.7 (CH), 73.8 (CH), 72.2, 70.5 (CH), 69.3 (CH_2), 67.4 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 37.8 (CH_2), 35.8 (CH), 34.0 (CH_2), 33.8 (CH_2), 20.7 (CH_2), 13.9 (CH_3); *m/z* (ES) 657.3407 $[M + H]^+$, $C_{40}H_{49}O_8$ requires 657.3427.

41. R_f: = 0.32 (60% diethyl ether in petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3695, 3556, 2957, 2934, 2871, 2839, 1612, 1585, 872. δ_H (400 MHz, $CDCl_3$) 7.28–7.16 (8H, m, 6 × Ar-*H*, 2 × Fur-*H*), 6.90–6.84 (6H, m, 6 × Ar-*H*), 5.85 (1H, dd, *J* = 6.4, 6.1 Hz, C=C*H*CH_2O), 4.72 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.60 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.47–4.38 (3H, m, OCH_2Ar, CH_2OCH_2Ar) 4.31 (1H, br s, C*H*OH), 4.30–4.15 (4H, m, OCH_2Ar, OCH_2Ar, CH=CC*H*O), 3.82 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.63 (1H, s, CHC*H*OCH_2Ar), 3.33 (1H, d, *J* = 15.6 Hz, CH_2C=CH), 3.25 (1H, d, *J* = 15.6 Hz, CH_2C=CH), 2.82 (1H, dd, *J* = 7.2, 7.2 Hz, C*H*CH_2CH_2), 2.15 (1H, ddd, *J* = 15.8, 5.3, 2.1 Hz, CHCH_2CH), 2.06 (1H, d, *J* = 4.2 Hz, CHO*H*), 1.80 (1H, ddd, *J* = 15.8, 6.8, 3.2 Hz, CHCH_2CH), 1.70–1.57 (2H, m, CHCH_2CH_2), 1.27–1.19 (2H, m, CH_2CH_3), 0.84 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 159.3 (C), 159.1 (C), 141.3 (CH), 141.1 (C), 139.7 (CH), 131.2 (C), 130.7 (C), 130.4 (C), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 124.4 (C), 123.3 (C), 113.9 (CH), 113.8 (CH), 113.8 (CH), 82.3 (CH), 73.6 (CH), 73.0 (CH_2), 72.3 (CH_2), 71.3 (CH), 69.8 (CH_2), 66.6 (CH_2), 55.4 (CH_3), 37.3 (CH_2), 37.2 (CH), 36.9 (CH_2), 31.4 (CH_2), 20.7 (CH_2), 14.1 (CH_3); *m/z* (ES) 679.3227 $[M + Na]^+$, $C_{40}H_{48}NaO_8$ requires 679.3247.

(4*S**,5*S**,8*R**,9*Z*)-5,8-Bis[(4-methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]ethylidene}-4-propyl-4,5,7,8,9,10-hexahydro-6*H*-cyclonona[*c*]furan-6-one 42

4 Å Molecular sieves (20 mg), TPAP (3.0 mg, 0.0085 mmol) and NMO (15.0 mg, 0.128 mmol) were added to a stirred solution of the alcohol **41** (56.0 mg, 85.4 μmol) in dichloromethane (2 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 16 h then concentrated to afford the crude ketone product as a black residue. Purification by flash column chromatography on silica gel (30 → 40% diethyl ether in hexane) yielded the pure ketone **42** as a colourless oil (44.5 mg, 80%): R_f: = 0.32 (60% diethyl ether in petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2935, 2863, 2838, 1720, 1613, 1586, 908, 870, 834; δ_H (400 MHz, $CDCl_3$) 7.30–7.19 (8H, m, 6 × Ar-*H*, 2 × Fur-*H*), 6.91–6.85 (6H, m, 6 × Ar-*H*), 5.81 (1H, dd, *J* = 8.0, 4.4 Hz, C=C*H*CH_2O), 4.71 (1H, d, *J* = 11.7 Hz, OCH_2Ar), 4.59 (1H, dd, *J* = 9.5, 6.7 Hz, CH_2C*H*OCH_2Ar), 4.49–4.43 (3H, m, OCH_2Ar, OCH_2Ar), 4.26 (1H, dd, *J* = 12.5, 8.0 Hz, CH_2OCH_2Ar), 4.20 (1H, d, *J* = 11.7 Hz, OCH_2Ar), 4.19 (1H, d, *J* = 11.3 Hz, OCH_2Ar), 4.01 (1H, dd, *J* = 12.5, 4.4 Hz, CH_2OCH_2Ar), 3.95 (1H, d, *J* = 2.7 Hz, OCC*H*OCH_2Ar), 3.82 (6H, s, 2 × OCH_3), 3.81 (3H, s, OCH_3), 3.37–3.29 (1H, m, C*H*CH_2CH_2), 3.23 (1H, br s, OCCH_2), 3.17–3.01 (2H, m, CH=CCH_2), 2.68–2.58 (1H, m, OCCH_2), 1.74–1.62 (2H, m, CHCH_2CH_2), 1.28–1.08 (2H, m, CH_2CH_3), 0.86 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 207.7 (C), 159.4 (C), 159.3 (C), 159.3 (C), 141.9 (CH), 139.5 (CH), 137.5 (C), 132.6 (CH), 130.5 (C), 130.3 (C), 129.9 (C), 129.7 (CH), 129.5 (CH), 129.5 (CH), 129.4 (CH), 124.0 (C), 122.1 (C), 113.9 (CH), 113.8 (CH), 84.5 (CH), 72.6 (CH_2), 72.2 (CH), 71.8 (CH_2), 69.5 (CH_2), 66.2 (CH_2), 55.3 (CH_3), 42.7 (CH_2), 36.6 (CH), 34.6 (CH_2), 24.5 (CH_2), 20.7 (CH_2), 14.0 (CH_3); *m/z* (ES) 677.3070 $[M + Na]^+$, $C_{40}H_{46}NaO_8$ requires 677.3090.

(4*S**,5*S**,8*R**,9*Z*)-5,8-Dihydroxy-9-(2-hydroxyethylidene)-4-propyl-4,5,7,8,9,10-hexahydro-1*H*-cyclonona[*c*]furan-1,3,6-trione (5-*epi*-hydroxycornexistin) 44

Rose Bengal (0.4 mg, 0.3 μmol) and diisopropylethylamine (11 μL, 0.063 mmol) were added to a stirred solution of the furan **42** in dichloromethane (1 mL) and the solution was cooled to −78 °C. Oxygen was bubbled through the pink solution for 5 min at −78 °C. The solution was stirred for a further 5 min and then sealed. The solution was then irradiated with a 500 W tungsten incandescent lamp for 30 min. Further diisopropylethylamine (11 μL, 0.063 mmol) was added to the reaction mixture and it was allowed to warm slowly to room temperature over 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride (5 mL) and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to afford the crude product mixture as a pale yellow oil. The compound was sufficiently pure to use without further purification.

4 Å Molecular sieves (10 mg) and TPAP (16.0 mg, 0.0455 mmol) were added to a stirred solution of the crude oxidation product (~0.03 mmol) in dichloromethane (1 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 2 h then filtered through a short plug of silica gel eluting with ethyl acetate to afford a pale yellow oil. To a solution of this oil in dichloromethane (1 mL), were added water (200 μL) and DDQ (20.6 mg, 0.0909 mmol). The deprotection reaction was monitored by analysis of reaction aliquots by mass spectrometry and the mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate (5 mL) when analysis indicated that all three of the PMB protecting groups had been removed (~4 h). The phases were separated and the aqueous phase was washed with dichloromethane (3 × 5 mL), acidified to pH 2 with a 1 M HCl solution and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to afford the crude product as a pale yellow oil. Purification of the product by reverse phase preparative HPLC (0 → 100% acetonitrile in water) yielded the pure triol **44** as a colourless solid (1.0 mg, 10% over 3 steps): mp 62–65 °C; ν_{max} (film)/cm^{-1} 3385, 2959, 2926, 2873, 2855, 1832, 1766, 1714, 1643, 1574, 924, 780, 752; δ_H (500 MHz, CD_3CN) 5.86 (1H, dd, *J* = 6.5, 5.9 Hz, C=C*H*), 4.99 (1H, dd, *J* = 10.3, 6.2 Hz, CH_2C*H*OH), 4.43–4.41 (1H, m, CHC*H*OH), 4.16–4.14 (2H, m, CH_2OH), 3.71 (1H, ddd, *J* = 8.9, 6.2, 2.5 Hz, C*H*CH_2CH_2), 3.50 (1H, d, *J* = 4.9 Hz, O*H*), 3.38 (1H, dd, *J* = 16.5, 10.3 Hz, CH_2CO), 3.34 (1H, br s, O*H*), 3.22 (1H, d, *J* = 14.3 Hz, CH_2OH), 3.12 (1H, dd, *J* = 14.3, 1.1 Hz, CH_2OH), 2.85 (1H, br s, O*H*), 2.71 (1H, dd, *J* = 16.5, 6.2 Hz, CH_2CO), 2.30–2.21 (1H, m, CHCH_2CH_2), 1.92–1.86 (1H, m, CHCH_2CH_2), 1.41–1.27 (2H, m, CH_2CH_3), 0.95 (3H, t, *J* = 7.4 Hz, CH_3); δ_C (125 MHz, CD_3CN) 210.2 (C), 166.8 (C), 165.1 (C), 147.4 (C), 141.2 (C), 137.6 (C), 136.4 (CH), 79.4 (CH), 66.5 (CH), 58.4 (CH_2), 42.9 (CH_2), 41.0 (CH), 31.2 (CH_2), 25.2 (CH_2), 21.6 (CH_2), 14.3 (CH_3); *m/z* (ES) 347.1095 $[M + Na]^+$, $C_{16}H_{20}NaO_7$ requires 347.1107.

Acetic acid (4*S,5*S**,6*R**,7a*R**)-5-acetoxy-9-oxo-4-propyl-5,6,7,7a,9,11-hexahydro-4*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-6-yl ester 45 and acetic acid (4*S**,5*S**,6*R**,7a*R**)-5-hydroxy-9-oxo-4-propyl-5,6,7,7a,9,11-hexahydro-4*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-6-yl ester 46**

A solution of triethylamine (100 μL of a 0.77 M solution in dichloromethane, 0.077 mmol), DMAP (0.9 mg, 8 μmol) and a solution of freshly distilled acetic anhydride (100 μL of a 0.64 M solution in dichloromethane, 0.064 mmol) were added to a stirred solution of the diol **35** (18.7 mg, 0.0640 mmol) in dichloromethane (1 mL) at 0 °C under argon. The reaction was allowed to warm to room temperature and the mixture was stirred for 3 h. The reaction mixture was poured into water (5 mL) and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to afford the crude product mixture as a pale yellow oil. Purification by flash column chromatography on silica gel (20 → 45% ethyl acetate in hexane) yielded the diacetate **45** (4.2 mg, 20%) as a colourless solid and the acetate **46** as a colourless oil (14.0 mg, 64%).

45. Mp 157–159 °C; R_f: = 0.52 (ethyl acetate–petroleum ether, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2930, 2873, 1747, 1631, 1602, 950, 917, 897, 870; δ_H (400 MHz, $CDCl_3$) 7.35 (1H, s, Fur-*H*), 7.23 (1H, d, *J* = 1.3 Hz, Fur-*H*), 6.20 (1H, s, COC*H*=C), 5.34 (1H, s, CHC*H*OAc), 4.96 (1H, s, CH=CC*H*O), 4.60–4.56 (1H, m, CH_2CHOAc), 3.85 (1H, d, *J* = 18.7 Hz, CH_2C=CH), 3.76 (1H, d, *J* = 18.7 Hz, CH_2C=CH), 2.55 (1H, dd, *J* = 9.0, 6.4 Hz, C*H*CH_2CH_2), 2.13 (3H, s, COCH_3), 1.99–1.94 (2H, m, CHCH_2CH), 1.96 (3H, s, COCH_3), 1.59–1.46 (2H, m, CHCH_2CH_2), 1.33–1.24 (2H, m, CH_2CH_3), 0.84 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 171.5 (C), 170.4 (C), 169.8 (C), 167.7 (C), 142.4 (CH), 140.2 (CH), 122.8 (C), 120.3 (CH), 118.8 (C), 81.7 (CH), 72.8 (CH), 68.8 (CH), 36.8 (CH_2), 35.6 (CH), 30.9 (CH_2), 23.8 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.3 (CH_2), 13.8 (CH_3); *m*/*z* (ES) 377.1588 $[M + H]^+$, $C_{20}H_{25}O_7$ requires 377.1600.

46. R_f: = 0.36 (ethyl acetate–petroleum ether, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3615, 2958, 2873, 1758, 1631, 975, 945, 908, 870; δ_H (400 MHz, $CDCl_3$) 7.35 (1H, dd, *J* = 1.6, 1.1 Hz, Fur-*H*), 7.33 (1H, d, *J* = 1.6 Hz, Fur-*H*), 6.19 (1H, s, COC*H*=C), 4.98–4.94 (1H, m, CH=CC*H*O), 4.58 (1H, ddd, *J* = 3.6, 3.6, 1.9 Hz, C*H*OAc), 3.89 (1H, br s, C*H*OH), 3.84 (1H, ddd, *J* = 18.5, 1.6, 1.1 Hz, CH_2C=CH), 3.74 (1H, br d, *J* = 18.5 Hz, CH_2C=CH), 2.48 (1H, dd, *J* = 9.5, 6.0 Hz, C*H*CH_2CH_2), 2.06 (3H, s, COCH_3), 1.89 (1H, d, *J* = 3.6 Hz, CHCH_2CH), 1.88 (1H, d, *J* = 3.6 Hz, CHCH_2CH), 1.78–1.58 (3H, m, CHCH_2CH_2, O*H*), 1.34–1.20 (2H, m, CH_2CH_3), 0.87 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 171.7 (C), 169.5 (C), 167.9 (C), 142.6 (CH), 140.5 (CH), 122.5 (C), 120.2 (CH), 118.8 (C), 81.8 (CH), 72.9 (CH), 70.8 (CH), 37.1 (CH_2), 36.9 (CH), 30.5 (CH_2), 23.8 (CH_2), 21.3 (CH_3), 20.5 (CH_2), 13.9 (CH_3); *m*/*z* (CI, NH_3) 334.1414 $[M]^+$, $C_{18}H_{22}O_6$ requires 334.1416.

Acetic acid (4*S,6*R**,7a*R**)-5,9-dioxo-4-propyl-5,6,7,7a,9,11-hexahydro-4*H*-2,8-dioxadicyclopenta[*a*,*d*]cyclononen-6-yl ester 48**

Dess–Martin periodinane (10 mg, 0.024 mmol) was added in one portion to a stirred solution of the alcohol **46** (8.0 mg, 0.024 mmol) in dichloromethane (1 mL) at room temperature under argon. The resultant suspension was stirred at room temperature for 5 h before addition of more Dess–Martin periodinane (20 mg, 0.048 mmol). Stirring was continued for 16 h and a saturated aqueous solution of sodium thiosulfate (1 mL) was then added. After the mixture had been stirred for 1 h, the aqueous phase was extracted with dichloromethane (2 × 2 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to afford the crude product as a pale yellow solid. Purification by flash column chromatography on silica gel (10 → 35% ethyl acetate in hexane) yielded the pure ketone **48** as a colourless oil (7.6 mg, 95%): R_f: = 0.27 (petroleum ether–ethyl acetate, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2874, 1757, 1634, 953, 909, 872; δ_H (400 MHz, $CDCl_3$) 7.40 (1H, d, *J* = 1.6 Hz, Fur-*H*), 7.32 (1H, m, Fur-*H*), 5.98 (1H, s, COC*H*=C), 5.10 (1H, d, *J* = 7.5 Hz, CH=CC*H*O), 5.02 (1H, dd, *J* = 4.2, 3.6 Hz, C*H*OAc), 3.80 (1H, d, *J* = 15.7 Hz, CH_2C=CH), 3.74 (1H, dd, *J* = 7.3, 7.3 Hz, C*H*CH_2CH_2), 3.36 (1H, d, *J* = 15.7 Hz, CH_2C=CH), 2.27 (1H, ddd, *J* = 16.1, 4.2, 1.7 Hz, CHCH_2CH), 2.15 (3H, s), 2.19–1.98 (2H, m, CHCH_2CH, CHCH_2CH_2), 1.60–1.51 (1H, m, CHCH_2CH_2), 1.33–1.23 (2H, m, CH_2CH_3), 0.92 (3H, t, *J* = 7.3 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 205.0 (C), 171.8 (C), 170.6 (C), 169.4 (C), 142.3 (CH), 142.1 (CH), 121.0 (C), 118.8 (C), 117.7 (CH), 79.2 (CH), 74.4 (CH), 45.9 (CH), 34.1 (CH_2), 33.1 (CH_2), 23.0 (CH_2), 20.5 (CH_3), 20.3 (CH_2), 13.9 (CH_3); *m*/*z* (ES) 333.1328 $[M + H]^+$, $C_{18}H_{21}O_6$ requires 333.1338.

(4*S,5*S**,6*R**,7a*R**)-(5,6-Methylenedioxy)-4-propyl-5,6,7,7a-tetrahydro-4*H*,11*H*,-2,8-dioxadicyclopenta[*a*,*d*]cyclononene-9-one 49**

p-Toluenesulfonic acid monohydrate (20.7 mg, 0.109 mmol) and 2,2-dimethoxypropane (402 μL, 3.30 mmol) were added to a stirred solution of the diol **35** (319 mg, 1.09 mmol) in dichloromethane (11 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 1.5 h, then poured into water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL) and the organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude product as a pale yellow solid. Purification by flash column chromatography on silica gel (10 → 40% ethyl acetate in petroleum ether) yielded the pure acetonide **49** as a colourless solid (356 mg, 98%): mp 158–160 °C (Found: C, 68.42; H, 7.34; $C_{19}H_{24}O_5$ requires: C, 68.66; H, 7.28%); R_f: = 0.34 (petroleum ether-ethyl acetate, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2934, 2872, 1750, 1632, 981, 961, 890, 872; δ_H (400 MHz, $CDCl_3$) 7.35 (1H, d, *J* = 1.5 Hz, Fur-*H*), 7.30 (1H, dd, *J* = 1.5, 1.5 Hz, Fur-*H*), 6.06 (1H, s, COC*H*=C), 4.89 (1H, d, *J* = 4.5 Hz, CH=CC*H*O), 4.08 (1H, d, *J* = 4.8 Hz, CHC*H*O), 3.91–3.84 (2H, m, CH_2C=CH, CH_2CHO), 3.62 (1H, d, *J* = 17.6 Hz, CH_2C=CH), 2.63 (1H, ddd, *J* = 10.1, 5.3, 1.5 Hz, C*H*CH_2CH_2), 1.95 (1H, dd, *J* = 15.5, 5.2 Hz, CHCH_2CH), 1.82–1.59 (3H, m, CHCH_2CH, CHCH_2CH_2), 1.32 (3H, s, CCH_3), 1.32–1.21 (2H, m, CH_2CH_3), 1.28 (3H, s, CCH_3), 0.88 (3H, t, *J* = 7.3 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 172.1 (C), 169.3 (C), 142.5 (CH), 138.9 (CH), 123.7 (C), 118.9 (CH), 118.6 (C), 107.4 (C), 82.0 (CH), 78.0 (CH), 72.4 (CH), 38.8 (CH_2), 34.1 (CH_2), 33.0 (CH), 28.2 (CH_3), 26.1 (CH_3), 24.8 (CH_2), 20.7 (CH_2), 13.9 (CH_3); *m*/*z* (EI) 332.1639 $[M]^+$, $C_{19}H_{24}O_5$ requires 332.1624.

(3a*R,5*R**,6*Z*,11*S**,11a*S**)-6-(2-Hydroxyethylidene)-2,2-dimethyl-11-propyl-4,5,6,7,11,11a-hexahydro-3a*H*-furo[3′,4′:4,5]cyclonona[1,2-*d*][1,3]dioxol-5-ol 50**

A solution of diisobutylaluminium hydride (1.2 mL of a 1.5 M solution in toluene, 1.8 mmol) was added dropwise to a stirred solution of the lactone **49** (296 mg, 0.891 mmol) in THF (10 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 2 h before dropwise addition of a solution of lithium aluminium hydride (1.8 mL of 1.0 M solution in THF, 1.8 mmol). The reaction mixture was allowed to warm slowly to room temperature then stirred for 16 h. The reaction was quenched by careful addition of methanol (2 mL), the mixture was then poured into a saturated aqueous solution of potassium sodium tartrate (10 mL) and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$) and concentrated to afford the crude product as a pale yellow oil. Purification by flash column chromatography on silica gel (30 → 70% ethyl acetate in petroleum ether) yielded the pure diol **50** as a colourless foam (221 mg, 74%): mp 122–124 °C; R_f: = 0.36 (ethyl acetate–petroleum ether, 2 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3611, 3488, 2958, 2933, 2872, 1715, 908, 872; δ_H (500 MHz, $CDCl_3$) 7.22 (1H, s, Fur-*H*), 7.15 (1H, s, Fur-*H*), 5.78 (1H, dd, *J* = 6.8, 6.0 Hz, C=C*H*CH$_2$), 4.48 (1H, dd, J = 11.9, 6.8 Hz, CH$_2$OH), 4.37 (1H, dd, *J* = 10.3, 5.4 Hz, C*H*OH), 4.28 (1H, s, CH$_2$C*H*O), 4.19–4.12 (2H, m, CH$_2$OH, CHC*H*O), 3.48 (2H, br s, 2 × O*H*), 3.34 (1H d, *J* = 15.4 Hz, CH$_2$C=CH), 3.22 (1H, d, *J* = 15.4 Hz, CH$_2$C=CH), 3.10 (1H, br s, C*H*CH$_2$CH$_2$), 1.84–1.52 (4H, m, CHCH$_2$CH, CHCH$_2$CH$_2$), 1.33 (3H, s, CC*H*$_3$), 1.31–1.21 (2H, m, CH$_2$CH$_3$), 1.25 (3H, s, CC*H*$_3$), 0.86 (3H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 142.0 (C), 142.0 (CH), 138.4 (CH), 127.7 (CH), 124.1 (C), 122.2 (C), 107.0 (C), 79.2 (CH), 75.1 (CH), 71.3 (CH), 58.9 (CH$_2$), 39.6 (CH$_2$), 38.6 (CH$_2$), 33.1 (CH), 33.1 (CH$_2$), 27.9 (CH$_3$), 26.0 (CH$_3$), 20.8 (CH$_2$), 13.9 (CH$_3$); *m*/*z* (ES) 359.1812 [M + Na]$^+$, $C_{19}H_{28}NaO_5$ requires 359.1834.

(3a*R,5*R**,6*Z*,11*S**,11a**S*)-5-[(4-Methoxybenzyl)oxy]-6-{2-[(4-methoxybenzyl)oxy]ethylidene}-2,2-dimethyl-11-propyl-4,5,6,7,11,11a-hexahydro-3a*H*-furo[3′,4′:4,5]cyclonona[1,2*d*][1,3]-dioxole 51**

Tetra-*n*-butylammonium iodide (11.0 mg, 0.298 mmol), *p*-methoxybenzyl chloride (95 μL, 0.70 mmol) and sodium hydride (60% dispersion in mineral oil, 60 mg, 1.4 mmol) were added to a stirred solution of the diol **50** (101 mg, 0.300 mmol) in DMF (4 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 30 min then warmed to room temperature and stirred for a further 3 h. The reaction was quenched by dropwise addition of water (10 mL) and the mixture was then diluted with diethyl ether (10 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The organic layers were combined, washed with a saturated aqueous solution of copper sulfate (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude product as a yellow oil. Purification by flash column chromatography on silica gel (0 → 30% ethyl acetate in hexane) yielded the pure acetonide **51** as a colourless oil (128 mg, 74%) (Found: C, 72.87; H, 7.83; $C_{35}H_{44}O_7$ requires C, 72.89; H, 7.69%); R_f: = 0.34 (petroleum ether–ethyl acetate, 4 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 2862, 2838, 1731, 1613, 1586, 907, 872; δ_H (400 MHz, $CDCl_3$) 7.26–7.20 (5H, m, Fur-*H*, 4 × Ar-*H*), 7.15 (1H, s, Fur-*H*), 6.88 (2H, d, *J* = 8.6 Hz, 2 × Ar-*H*), 6.86 (2H, d, *J* = 8.7 Hz, 2 × Ar-*H*), 5.77 (1H, dd, *J* = 6.3, 6.2 Hz, C=C*H*CH$_2$), 4.44–4.40 (3H, m, CH$_2$Ar, CH$_2$Ar), 4.34 (1H, ddd, *J* = 9.8, 5.7, 3.0 Hz, CH$_2$C*H*O), 4.25–4.15 (4H, m, CHC*H*O, CH$_2$OCH$_2$Ar, CH$_2$Ar), 4.05 (1H, br s, C*H*OCH$_2$Ar), 3.82 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.37 (1H, dd, *J* = 9.4, 5.4 Hz, C*H*CH$_2$CH$_2$), 3.29 (1H d, *J* = 14.6 Hz, CH$_2$C=CH), 3.21 (1H, d, *J* = 14.6 Hz, CH$_2$C=CH), 1.76–1.55 (4H, m, CHCH$_2$CH, CHCH$_2$CH$_2$), 1.34 (3H, s, CC*H*$_3$), 1.32–1.18 (2H, m, CH$_2$CH$_3$), 1.28 (3H, s, CC*H*$_3$), 0.83 (3H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 159.3 (C), 159.1 (C), 141.8 (CH), 138.1 (CH), 130.5 (C), 130.4 (C), 129.5 (CH), 129.0 (CH), 127.1 (CH), 124.6 (C), 123.4 (C), 113.9 (CH), 113.8 (CH), 106.5 (C), 79.2 (CH), 77.3 (CH), 75.5 (CH), 72.4 (CH$_2$), 70.1 (CH$_2$), 66.5 (CH$_2$), 55.3 (CH$_3$), 39.0 (CH$_2$), 36.2 (CH$_2$), 33.2 (CH), 31.7 (CH$_2$), 27.9 (CH$_3$), 25.7 (CH$_3$), 20.7 (CH$_2$), 13.9 (CH$_3$); *m*/*z* (EI) 576.3091 [M]$^+$, $C_{35}H_{44}O_7$ requires 576.3087.

(4*S,5*S**,6*R**,8*R**,9*Z*)-8-[(4-Methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]ethylidene}-4-propyl-5,6,7,8,9,10-hexahydro-4*H*-cyclonona[*c*]furan-5,6-diol 52**

p-Toluenesulfonic acid monohydrate (4.2 mg, 22 μmol) was added to a stirred solution of the acetonide **51** (128 mg, 0.222 mmol) in methanol (15 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 16 h, then poured into a saturated aqueous solution of sodium hydrogen carbonate (10 mL). The mixture was diluted with water (10 mL) and the aqueous phase was extracted with dichloromethane (5 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated to afford the crude diol as a pale yellow oil. Purification by flash column chromatography on silica gel (20 → 60% ethyl acetate in petroleum ether) yielded the pure diol **52** (64.8 mg, 54%) and the original acetonide **51** (24.0 mg, 19%) as colourless oils: R_f: = 0.24 (petroleum ether–ethyl acetate, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3563, 2957, 2933, 2862, 2838, 1613, 1586, 870; δ_H (400 MHz, $CDCl_3$) 7.27 (1H, s, Fur-*H*), 7.24 (1H, s, Fur-*H*), 7.23–7.18 (4H, m, 4 × Ar-*H*), 6.88 (2H, d, *J* = 8.0 Hz, 4 × Ar-*H*), 6.86 (2H, d, *J* = 8.5 Hz, 4 × Ar-*H*), 5.86 (1H, dd, *J* = 6.0, 5.9 Hz, C=C*H*CH$_2$), 4.46–4.41 (2H, m, CH$_2$Ar), 4.44 (1H, d, *J* = 11.5 Hz, CH$_2$Ar), 4.32–4.29 (2H, m, CH$_2$OCH$_2$Ar), 4.28 (1H, d, *J* = 11.5 Hz, CH$_2$Ar), 4.03 (1H, dd, *J* = 4.4, 4.3 Hz, C*H*OCH$_2$Ar), 3.98 (1H, dd, *J* = 6.0, 1.9 Hz, CH$_2$C*H*OH), 3.82–3.81 (1H, m, CHC*H*OH), 3.82 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.30 (1H, d, *J* = 15.5 Hz, CH$_2$C=CH), 3.23 (1H, d, *J* = 15.5 Hz, CH$_2$C=CH), 2.95 (1H, dd, *J* = 7.8, 7.7 Hz, C*H*CH$_2$CH$_2$), 1.84–1.61 (6H, m, CHCH$_2$CH, CHCH$_2$CH$_2$, 2 × O*H*), 1.35–1.26 (2H, m, CH$_2$CH$_3$), 0.88 (3H, t, *J* = 7.3 Hz, CH$_3$); δ_C (100 MHz, $CDCl_3$) 159.3 (C), 159.2 (C), 141.2 (CH), 140.2 (CH), 138.6 (C), 130.4 (C), 129.5 (CH), 129.4 (CH), 129.1 (CH), 123.5 (C), 122.9 (C), 113.9 (CH), 113.9 (CH), 76.2 (CH), 75.4 (CH), 72.4 (CH$_2$), 71.3 (CH), 70.1 (CH$_2$), 66.9 (CH$_2$), 55.4 (CH$_3$), 37.0 (CH$_2$), 36.3 (CH), 36.3 (CH$_2$), 32.0 (CH$_2$), 20.6 (CH$_2$), 13.9 (CH$_3$); *m*/*z* (EI) 536.2792 [M]$^+$, $C_{32}H_{40}O_7$ requires 536.2774.

(4*S,5*S**,6*R**,8*R**,9*Z*)-5-Hydroxy-8-[(4-methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]ethylidene}-4-propyl-5,6,7,8,9,10-hexahydro-4*H*-cyclonona[*c*]furan-6-yl acetate 53**

Triethylamine (22 μL, 0.16 mmol), DMAP (0.5 mg, 5 μmol) and freshly distilled acetic anhydride (5.2 μL, 0.055 mmol) were added

to a stirred solution of the diol **52** (27.9 mg, 0.519 mmol) in dichloromethane (1 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 30 min, then warmed to room temperature and stirred for a further 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride (5 mL) and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated to afford the crude product as a pale yellow oil. Purification by flash column chromatography on silica gel (0 → 30% ethyl acetate in hexane) yielded the acetate **53** as a colourless oil (19.7 mg, 65%): R_f: = 0.38 (petroleum ether–ethyl acetate, 1 : 1); ν_{max} ($CHCl_3$)/cm^{-1} 3541, 2958, 2934, 2863, 2838, 1730, 1613, 1586, 908, 870; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, J = 8.3 Hz), 7.21 (2H, m), 7.26 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.6 Hz), 5.90 (1H, dd, J = 5.9, 5.9 Hz), 5.29–5.25 (1H, m), 4.49–4.23 (6H, m), 3.98 (1H, dd, J = 4.3, 4.2 Hz), 3.88 (1H, d, J = 6.7 Hz), 3.81 (6H, s), 3.34–3.21 (2H, m), 2.99 (1H, dd, J = 8.0, 7.6 Hz), 2.02 (3H, s), 1.79–1.60 (4H, m), 1.36–1.26 (2H, m), 0.87 (3H, t, J = 7.3 Hz); δ_C (100 MHz, $CDCl_3$) 170.2 (C), 159.2 (C), 159.1 (C), 141.3 (CH), 140.4 (CH), 137.9 (C), 130.6 (C), 130.4 (C), 130.0 (CH), 129.6 (CH), 128.9 (CH), 123.1 (C), 122.9 (C), 113.8 (CH), 113.8 (CH), 75.4 (CH), 74.4 (CH), 73.6 (CH), 72.4 (CH_2), 69.9 (CH_2), 67.0 (CH_2), 55.3 (CH_3), 36.8 (CH), 36.7 (CH_2), 32.2 (CH_2), 31.6 (CH_2), 21.4 (CH_3), 20.6 (CH_2), 13.9 (CH_3); m/z (ES) 601.2757 [M + Na]$^+$, $C_{34}H_{42}NaO_8$ requires 601.2777.

(4*S**,6*R**,8**R*,9*Z*)-6,8-Bis[(4-methoxybenzyl)oxy]-9-{2-[(4-methoxybenzyl)oxy]ethylidene}-4-propyl-7,8,9,10-tetrahydro-4*H*-cyclonona[*c*]furan-5(6*H*)-one 56

4 Å Molecular sieves (20 mg), TPAP (2.6 mg, 7.3 μmol) and NMO (12.8 mg, 109 μmol) were added to a stirred solution of the alcohol **40** (47.8 mg, 72.9 μmol) in dichloromethane (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 h then concentrated to afford the crude ketone **56** as a black residue. Purification by flash column chromatography on silica gel (30 → 40% diethyl ether in hexane) yielded the pure ketone **56** as a colourless oil (39.4 mg, 83%): R_f: = 0.39 (60% diethyl ether in petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} ($CHCl_3$) 2959, 2936, 2862, 2838, 1721, 1613, 1586; δ_H (400 MHz, $CDCl_3$) 7.30–7.19 (8H, m, 6 × Ar-*H*, 2 × Fur-*H*), 6.89–6.83 (6H, m, 6 × Ar-*H*), 5.71–5.49 (1H, m, C=C*H*CH_2), 4.71 (1H, d, J = 11.1 Hz, CH_2Ar), 4.53 (1H, dd, J = 11.3, 4.6 Hz, CH=CC*H*O), 4.39–4.29 (4H, m, 2 × CH_2Ar), 4.16–4.11 (2H, m, CH_2Ar, CH_2OCH_2Ar), 3.98 (1H, dd, J = 5.9, 2.0 Hz, COCHC*H*O), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.78–3.73 (1H, m, CH_2OCH_2Ar), 3.69 (1H, dd, J = 7.7, 6.4 Hz, C*H*CH_2CH_2), 3.14 (1H, d, J = 16.1 Hz, CH=CCH_2), 3.01 (1H, d, J = 16.1 Hz, CH=CCH_2), 2.68 (1H, ddd, J = 14.5, 11.3, 2.0 Hz, CHCH_2CH), 2.39 (1H, ddd, J = 14.5, 5.9, 4.6 Hz, CHCH_2CH), 1.82–1.69 (2H, m, CHCH_2CH_2), 1.35–1.21 (2H, m, CH_2CH_3), 0.92 (3H, t, J = 7.3 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 209.3 (C), 159.4 (C), 159.3 (C), 159.2 (C), 141.3 (CH), 140.5 (CH), 136.0 (CH), 135.0 (C), 130.7 (C), 130.5 (C), 130.2 (C), 129.7 (CH), 129.6 (CH), 129.5 (CH), 123.4 (C), 123.2 (C), 113.9 (CH), 113.9 (CH), 113.8 (CH), 82.4 (CH), 72.6 (CH_2), 72.0 (CH_2), 71.9 (CH), 69.7 (CH_2), 66.5 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 42.7 (CH), 34.0 (CH_2), 33.0 (CH_2), 22.1 (CH_2), 21.2 (CH_2), 14.2 (CH_3); m/z (ES) 677.3061 [M + Na]$^+$, $C_{40}H_{46}NaO_8$ requires 677.3090.

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