The Total Synthesis of the Annonaceous Acetogenin, Muricatetrocin C

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Dedicated to Professor Jean-François Normant on the occasion of his 65th birthday

Abstract: The total synthesis of the potential antitumour agent muricatetrocin C has provided an ideal stage for the exploitation and development of new chemistry. A convergent synthetic strategy has been realised incorporating three distinct pieces of methodology, these include a highly diastereoselective hetero-Diels–Alder reaction to construct the butenolide terminus, an oxygen to carbon rearrangement to install the *trans*-2,5-disubstituted tetrahydrofuran ring and a spatial desymmetrisation process to afford the *anti*-diol unit.

Keywords: antitumor agents · cycloaddition · natural products · total synthesis

Introduction

In their quest for novel lead structures Cole and co-workers in 1982 isolated a new natural product, uvaricin (**1**), from the dried roots of *Uvaria accuminta* (Figure 1).[1] This was the first member of a family of natural products that has since come to be known as the annonaceous acetogenins and which now features over 350 members, isolated from 37 different species

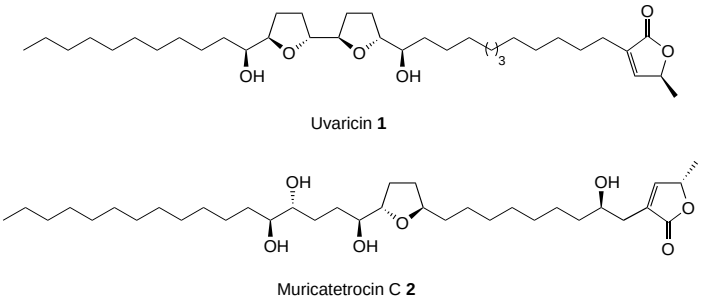

Figure 1. Uvaricin (**1**) and muricatetrocin C (**2**).

of *Annonaceae*.[2] The structure of **1** can be taken as typical of the annonaceous acetogenins. They are a series of C-35/C-37 natural products, usually characterised by a central polyoxygenated core comprising one, two or three tetrahydrofuranyl (THF) rings along with a number of flanking hydroxyl groups. Either side of this core unit is substituted with a long carbon chain, one bearing a terminal methyl substituted α,β-unsaturated γ-lactone ring, whilst the other side is simply aliphatic. The largest site of variation in the acetogenins is the central core, where the ring(s) can be *cis*- or *trans*-disubstituted, adjacent or nonadjacent, flanked by one or two hydroxyl groups or incorporate other functionality such as a ketone, epoxide or THP ring.

These compounds are known to exhibit a broad range of biological activities, the precedent for which came from early South American populations, who used extracts of *Annonaceae* plants as pesticidal and antiparasitic agents.[3] The tested activities of the acetogenins now include, but are not limited to: pesticidal, antifeedant, antiprotozoal, immunosuppressive and probably most importantly, antitumour.[4] In this respect they are known to be very potent cytotoxic compounds, targeting the reduced nicotinamide adenine dinucleotide (NADH), ubiquinone oxidoreductase in complex I, which is a membrane bound protein of the mitochondrial electron transport system, and the ubiquinone linked NADH oxidase in the plasma membrane of cancerous cells.[5, 6] Inhibition by these mechanisms results in ATP deprivation, which leads to apoptosis of the high energy demanding tumour cells.[7] The acetogenins are now considered as the most potent (effective in nanomolar concentrations) known inhibitors of mitochondrial complex I.[5, 8] More recently the annonaceous acetogenins have also been shown to overcome resistance in multidrug resistant (MDR) tumours.[9] Thus, for the above reasons and by virtue of their limited availability from natural sources, these compounds have been targeted for total synthesis by a number of research groups.[10–15]

Muricatetrocin C (**2**) was isolated in 1996 by McLaughlin et al. from the leaves of *Rollina mucosa*, a tropical fruit tree native to the West Indies and parts of Central America.[16] Our specific interest in this molecule stemmed from two factors. Firstly, the isolation group showed that **2** exhibits potent

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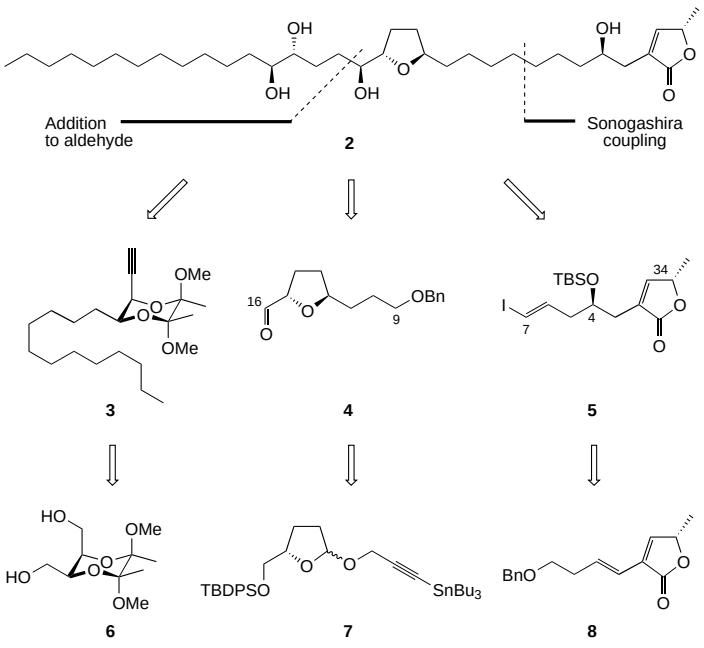
inhibitory action against PC-3 prostatic adenocarcinoma, PACA-2 pancreatic carcinoma and A-549 lung carcinoma cell lines, making it a potential antitumour agent. Unfortunately, the limited supply of the natural product (15 mg from 1.63 kg of dried leaves) restricted further investigation, highlighting the need for total synthesis in this area.[16] The second level of interest arose due to the structural features present in the molecule: namely seven stereogenic centres, compartmentalised into three distinct structural motifs. It was envisaged that **2** would provide an excellent platform for both the evolution of existing group methodology and the potential development of new synthetic tools. This was compounded by the fact that no synthesis of **2** had previously been reported in the literature.[17]

Synthetic plan: The strategy towards **2** centred on the enantioselective preparation of fragments **3**, **4** and **5**, and their subsequent coupling to realise an overall convergent route (Scheme 1). The plan incorporates some well-established endgame chemistry based on the large literature precedent in the area, whilst also generating three evenly



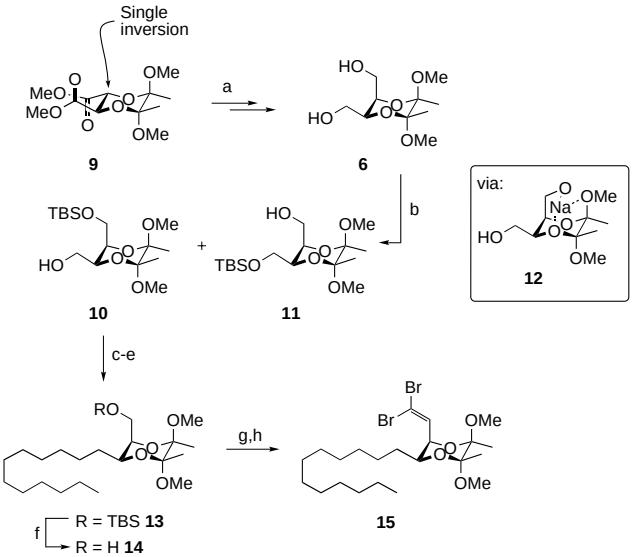
Scheme 1. Synthetic plan for **2**. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

functionalised fragments that it was hoped would allow either the utilisation of existing methodology from our laboratories or the development and application of new chemistry. Thus the key features of the approach are: the application of the recently reported (*R*′,*R*′,*R*,*S*)-2,3-butanediacetal-protected butane tetrol **6** as a building block for the *anti*-1,2-diol containing component **3** through selective chemical differentiation of the incongruous hydroxyl termini;[18] the use of the recently developed anomeric oxygen to carbon rearrangement of alkynyl stannanes such as **7** for the stereoselective construction of the 2,5-*trans*-disubstituted THF ring component **4**;[19] and finally the implementation of a new approach to the hydroxy-butenolide terminus **5**, using a hetero-Diels–Alder (HDA) reaction with diene **8** to simultaneously install the 1,5-stereochemical relationship and mask the butenolide double bond.

With regard to the later stages of the synthesis, addition of the alkynyl lithium reagent derived from **3** to the anomerically disposed aldehyde **4**, was envisaged to introduce the remaining stereogenic centre at C-16. Subsequent manipulation to unmask a terminal alkyne, would then allow for a Sonogashira coupling with **5** to complete the carbon skeleton. The formation of this C_7–C_8 bond and the subsequent selective hydrogenation of the resulting enyne in the presence of the butenolide is supported by good precedent from previous work carried out in this area.[20]

Results and Discussion

The *anti*-diol fragment: The synthesis commenced with the preparation of **3** wherein the *anti*-diol arises from the chemical desymmetrisation of a *meso*-dimethyltartrate derivative, following a modification of the previously reported process.[21] Thus 2,3-butanediacetal (BDA) protected (*R*,*R*)-dimethyl tartrate **9** was converted to the corresponding (*R*,*S*)-diol **6** exploiting the local chirality contained within the BDA protecting group (Scheme 2). Terminal differentiation of **6** by successive treatment with sodium hydride (1.1 equiv) then *tert*-butyldimethylchlorosilane (TBSCl) afforded **10** and **11** in a 5:1 ratio of easily separable diastereoisomers, favouring the axial silyl ether **10**. In order to achieve this bias towards axial protection it was critical to observe precipitation of the initially formed mono-anion. Presumably the nature of this precipitate is such that the sodium cation is positioned



Scheme 2. Synthesis of *gem*-dibromo olefin **15**. a) ref. [21]; b) NaH; THF/pentane, 0 °C → rt, 30 min, then TBSCl, 40 min (72 %); c) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 → rt; d) $CH_3(CH_2)_{10}PPh_3I$, *n*-BuLi, THF, −78 °C, 30 min (92 %, two steps; *Z*/*E* 8:1); e) Raney nickel, H_2, EtOH; rt, 30 min (90 %); f) TBAF, THF, rt, 2 h; g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 → 0 °C; h) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 30 min, (88 %, three steps). TBAF = tetra-*n*-butylammonium fluoride, TBSCl = *tert*-butyldimethylsilyl chloride.

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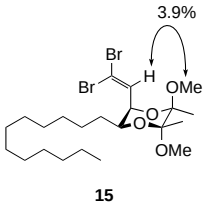
between the axial oxy-anion and a donating lone pair from one of the two oxygen atoms of the BDA dioxane ring. In this event a kinetic trap of the anion **12** with TBSCl *prior* to equilibration in solution would lead to the observed result. More conventional silylation conditions (namely TBSCl, imidazole, THF) afforded the expected equatorial silyl ether **11** with high diastereoselectivity (**11**/**10** 17:1).[18b]

Chain extension to build the twelve-carbon terminus was the first homologation that was required to progress towards fragment **3**. Oxidation of **10** to the equatorial aldehyde proceeded smoothly using the Swern conditions. This crude material underwent Wittig reaction with the phosphorus ylid derived from 1-iodoundecane at $-78\,^{\circ}C$ in THF, to form an inseparable mixture of olefins (*Z*/*E* 8:1) in good yield. For ease of subsequent characterisation, the resulting olefin was saturated using hydrogen and Raney nickel in ethanol, to afford **13**. Reduction with hydrogen in the presence of other metal additives such as palladium on carbon and platinum dioxide were far less efficient, producing significant decomposition of the starting material. This was perhaps a result of competing hydrogenolysis at the allylic position.

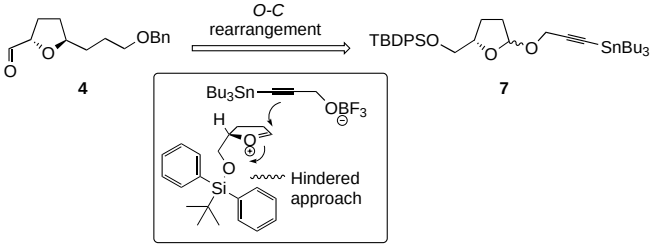
Deprotection of the silyl group using *tetra*-butylammonium fluoride (TBAF) in THF furnished **14**, then Swern oxidation of the resulting alcohol afforded the axial aldehyde. Conversion to a suitable coupling partner required a one-carbon homologation reaction. Thus, addition of the crude aldehyde to a solution of CBr_4 and Ph_3P in CH_2Cl_2 at $0\,^{\circ}C$, afforded *gem*-dibromo olefin **15** in good yield.[22] Compound **15** was subjected to a NOE study in order to ascertain whether any epimerisation had occurred either in the oxidation step or in the presence of the in situ generated (dibromomethylene)triphenylphosphorane. The important effect was observed between the olefin proton and the proximal axial methoxy substituent (Figure 2). The conversion of **15** to the alkynyl lithium derivative of **3** is described in the coupling section.



15

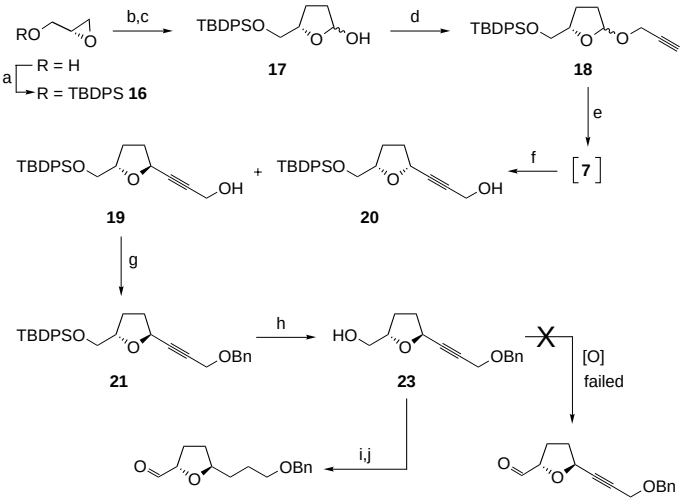
Figure 2. NOE to confirm axial disposition of the *gem*-dibromo olefin **15**.

The central fragment: The *trans*-relationship across the disubstituted tetrahydrofuran ring **4** was expected to arise from a Lewis acid mediated rearrangement of alkynyl stannane **7**, with the approach of the tributylstannane being directed by the pendant bulky *tert*-butyldiphenylsilyloxymethyl group (Scheme 3).



Scheme 3. Synthetic plan towards tetrahydrofuran **4**.

The known lactol **17** was readily prepared in three high yielding steps from (*R*)-glycidol (Scheme 4). Consequently, formation of the *tert*-butyldiphenylsilyl (TBDPS) ether **16**, opening of this epoxide with allyl magnesium bromide in the presence of catalytic dilithium tetrachlorocuprate [Li_2CuCl_4], and then ozonolysis of the resulting alkenol with in situ ring closing afforded **17** in 70% overall yield, as a 3:2 mixture of anomers. Subsequent treatment of this material with excess propargylic alcohol and catalytic Amberlyst A-15 in benzene at reflux delivered the propargylic ether **18** in excellent yield, again as a 3:2 mixture of anomers.



Scheme 4. Synthesis of tetrahydrofuran **4**. a) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, rt, 24 h (85%); b) allylMgBr, $CuLi_2Cl_4$, (10 mol%), THF, $-30\,^{\circ}C$ 2 h (89%); c) O_3, CH_2Cl_2, $-78\,^{\circ}C$, 20 min; PPh_3, $-78\,^{\circ}C \rightarrow$ rt, 14 h (93%); d) prop-2-yn-1-ol, Amberlyst A-15, benzene, reflux, 15 min (91%); e) *n*-BuLi, THF, $-78\,^{\circ}C$, 30 min; Bu_3SnCl, $-78\,^{\circ}C \rightarrow$ rt, 30 min; f) $BF_3 \cdot OEt_2$, CH_2Cl_2, $-10\,^{\circ}C$, 10 min [85%, two steps (5.5:1, **19**/**20**)]; g) KHMDS, $-78\,^{\circ}C$, 30 min, then BnBr, THF, $-78\,^{\circ}C \rightarrow$ rt (78%); h) TBAF, THF, rt, 3 h (95%); i) Raney nickel, H_2, EtOH; rt, 30 min (70%); j) DMSO, $(COCl)_2$, CH_2Cl_2, $-78\,^{\circ}C$; NEt_3, $-78 \rightarrow$ rt (used crude). TBDPSCl = *tert*-butyldiphenylsilylchloride, DMAP = dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide.

Subjection to the rearrangement protocol by deprotonation of the alkyne **18** with *n*-butyllithium in THF at $-78\,^{\circ}C$, followed by treatment with tributyltin chloride and warming to room temperature afforded, after aqueous work up, the crude tributylstannylated material **7**. This was not purified, but simply dissolved in dichloromethane, cooled to $-10\,^{\circ}C$ and then treated with boron trifluoride etherate for ten minutes before the reaction mixture was quenched with sodium hydroxide. Aqueous work up and inspection of the crude ^1H NMR indicated that the reaction had proceeded to give the carbon linked products **19** and **20** in a ratio of 5.5:1 favouring the *trans*-product **19** in good overall yield. Benzylation of the released primary hydroxyl by treatment with potassium hexamethyldisilazide (KHMDS) followed by benzyl bromide allowed chromatographic separation of the diastereoisomers to afford **21** [along with minor isomer (not shown) **22**], which underwent analysis by NOE to corroborate the predicted *trans*-relationship of the major component (Figure 3).[23]

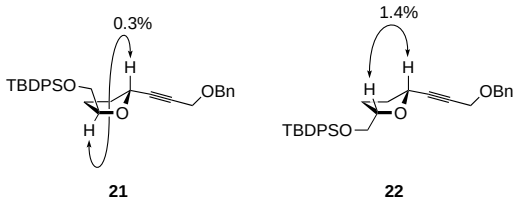


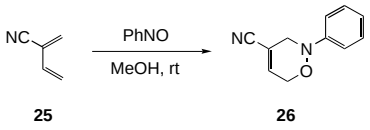
Figure 3. NOE values to confirm the stereochemical outcome of the *O*–*C* rearrangement reaction.

After the successful introduction of the C-12 stereogenic centre, **21** needed to be prepared for coupling with the metallated fragment **3**. Given that this coupling produces a further propargylic triple bond requiring reduction, it was thought that both these hydrogenation steps would be performed simultaneously, at a later stage in the synthesis. Therefore TBAF mediated removal of the silyl protecting group proceeded smoothly to afford **23**. However, trial reactions with a variety of common oxidation procedures revealed that the desired aldehyde **24**, was unstable and extremely difficult to isolate. Surprisingly, after much experimentation, it was found that removal of the triple bond by hydrogenation over Raney nickel allowed Swern oxidation to, and isolation of, essentially pure aldehyde **4**.

The butenolide terminus: The synthetic strategy towards **5** centred on the idea of utilising the C-34 methyl substituent of diene **8** to influence the introduction of the C-4 stereogenic centre—a formal 1,5-induction process (Scheme 5). This approach offers a significant departure from the previous work in the area, the majority of which concentrates on the union of two chiral fragments or the employment of more than one source of chirality.

The heterodienophile requires two distinct properties in order to render the reaction successful namely the necessary steric bulk to develop the unfavourable, nonbonding interaction with the C-34 methyl substituent and therefore control the facial selectivity of the reaction, and secondly in the case of X ≠ O; the desired frontier orbital coefficients to force the regioselective delivery of oxygen atom to C-4.

With these criteria in mind the obvious choice of dienophile, singlet oxygen (X = O), which avoids any regiochemical issues was considered unsuitable due to the lack of any steric component to direct the diastereoselectivity. A search for more appropriate alternatives indicated nitroso dienophiles as potential reagents. In particular nitrosobenzene, which along with the evident steric properties, had been shown by Kresze and Firl to exhibit promising regioselectivity, albeit in combination with the much simpler 2-cyanobutadiene **25**, affording **26** in 70% yield (Scheme 6).[24] With this initial precedent in hand, molecular orbital calculations were performed in an attempt to predict if the more complicated diene **8** would exhibit the same regiochemical preferences (Figure 4). The resulting frontier orbital coefficients implied that the reaction should proceed with normal electron demand to favour the desired regioisomer.[25]



Scheme 6. Reaction of nitrosobenzene with 2-cyanobutadiene (**25**).

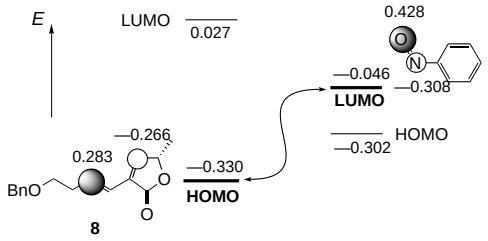
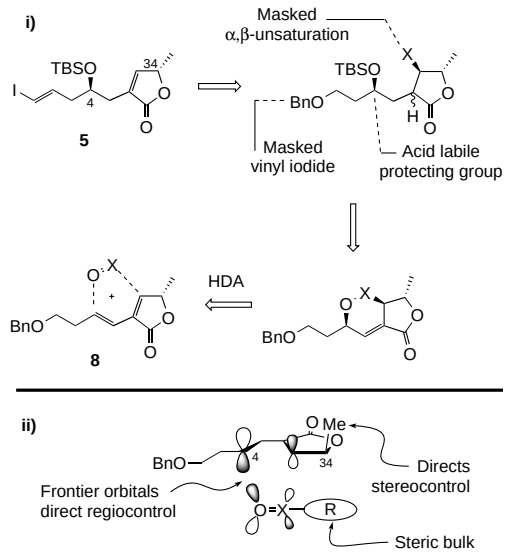


Figure 4. Results of the frontier orbital calculations.



Scheme 5. i) Synthetic plan towards fragment **5**; ii) requirements of the dienophile for the successful induction of stereochemistry.

Subsequent to the HDA reaction, two events are required, firstly elimination of the aryl amine portion to re-introduce the unsaturation to the γ-lactone, and then manipulation of the primary benzyl ether to allow one carbon homologation to a vinyl iodide. The important issue is that the cleavage of the N–O bond must be performed selectively in the presence of the benzyl group and more importantly the α,β-unsaturation, which is required to protect against the possibility of internal translactonisation. However, the synthetic ordering of the above events was considered interchangeable and this inherent flexibility was found to be an important benefit of the synthesis plan.

The synthesis began with 1,4-butanediol, which was monoprotected to give the primary benzyl ether **27**, then a tandem Swern–Wittig reaction afforded the α,β-unsaturated *tert*-butyl ester **28** in excellent yield (Scheme 7). Then, in a three step procedure with no isolation of intermediates, **28** was treated with LDA in the presence of HMPA followed by the addition of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal, derived from (*S*)-ethyl lactate.[26] This crude material was stirred

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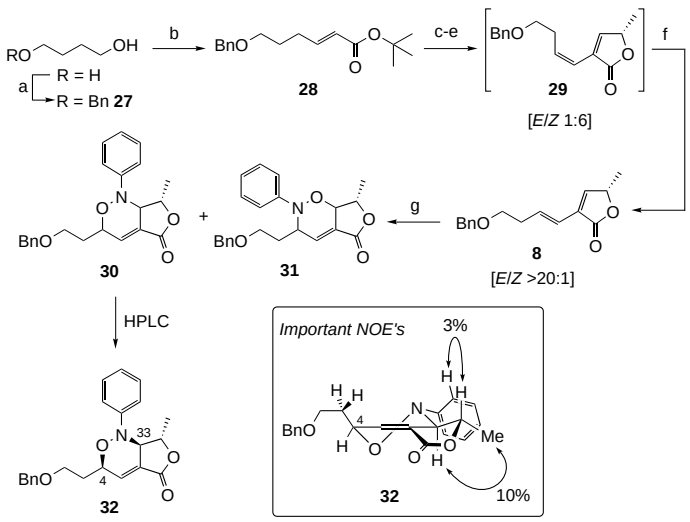
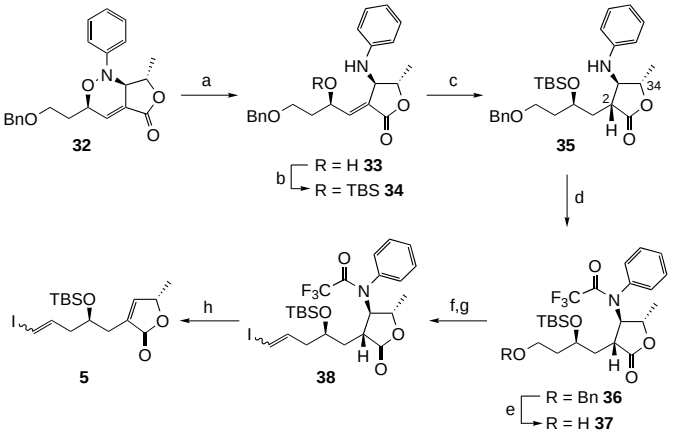


Scheme 7. Synthesis of the hetero-Diels–Alder adduct **32**. a) NaH; BnBr, DMF, 0 °C (82 %); b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 → rt, then (*tert*-butoxycarbonylmethylene)triphenylphosphorane, CH_2Cl_2, 0 °C → rt, 14 h (96 %); c) LDA/HMPA/THF, −78 °C, 30 min, then (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal, −78 → 0 °C; d) MeOH/HCl (sat.), rt, 5 min, (repeat); e) MsCl, NEt_3, CH_2Cl_2, 0 °C, 30 min (*E*/*Z* 1:6); f) I_2 (5 mol %), sunlamp irradiation, rt, 4 h (56 %, four steps; *E*/*Z*, >20:1); g) PhNO, MeOH/CH_2Cl_2 (1:1), 0 °C, 21 h [91 % (**30**/**31** 7:3)]; DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide, MsCl = methanesulfonyl chloride.

in an acidic methanol solution to effect deprotection of both the TBS group and the *tert*-butyl ester allowing cyclisation to the γ-lactone. β-Elimination was then achieved by treatment of the crude material with methanesulfonyl chloride and triethylamine to afford **29** and **8** as a mixture (*E*/*Z* 1:6) of geometric isomers at the external olefin position in 56 % over the three steps.[27] The desired *E*-isomer **8** was then accessed with a ratio of greater than 20:1 by sunlamp irradiation in the presence of a catalytic amount of iodine.[28]

With **8** now readily available, the key HDA reaction was investigated. It was found that overnight stirring of a methanol/dichloromethane (1:1) solution of **8** with nitrosobenzene at 0 °C afforded a mixture of regioisomers (**30**/**31** 7:3), favouring the desired adduct **30**, in overall 89 % yield. Pleasingly, inspection of the crude ^{1}H NMR showed that the major regioisomer **30** had been formed with a diastereoisomeric ratio of greater than 20:1—thus the observed diastereoselection appeared to be limited only by the original geometry of the external olefin in the diene precursor. The required diastereomerically pure regioisomer **32** was obtained in 55 % yield following separation by HPLC; the slightly diminished yield perhaps reflecting the propensity for retro-DA reaction on silica that has been previously documented for this class of compounds.[29] Extensive NOE studies were undertaken on the major isolated product **32** with the important enhancements being found between H-34 and the *ortho*-protons of the aryl amine portion, and between H-33 and the C-34 methyl substituent to confirm the regioselectivity and diastereoselectivity, respectively.

After screening a variety of standard conditions for the cleavage of N–O bonds with little success, it was found that freshly prepared $[Mo(CO)_3(MeCN)_3]$ in the presence of water could effect this transformation at ambient temperature, affording **33** in 70 % yield (Scheme 8).[30] Interestingly the direct use of $[Mo(CO)_6]$ in refluxing acetonitrile (the precursor to $[Mo(CO)_3(MeCN)_3]$) resulted in thermal decomposition of the HDA adduct to afford diene **8**—probably the result of a retro-Diels–Alder process. Subsequent silylation of the resultant secondary hydroxyl with TBSCl proceeded smoothly in 83 % yield to afford **34**. With the potential for translactonisation alleviated, the α,β-unsaturation was cleanly and efficiently removed by hydrogenation over catalytic platinum dioxide to afford **35**. This reduction step furnished a single diastereoisomer, which was subsequently shown by NOE analysis to have the (*R*)-configuration at C-2, with the important enhancement occurring between H-2 and H-34.



Scheme 8. Synthesis of the butenolide fragment **5**. a) $[Mo(CO)_6]$, MeCN, reflux, 4 h; then **32**, H_2O, rt, 15 min (70 %); b) TBSCl, imidazole, DMF, rt, 14 h (83 %); c) PtO_2 (33 mol %), H_2, MeOH; rt, 90 min (98 %); d) TFAA, Hünig's base, CH_2Cl_2, 0 °C, 30 min; e) $Pd(OH)_2$ (20 mol %), H_2, MeOH; rt, 48 h (90 % two steps); f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C → 0 °C; g) $CrCl_2$, CHI_3, THF, 0 °C → rt, 14 h (80 % two steps, *E*/*Z* 4:1); h) DBU, CH_2Cl_2, 0 °C, 60 min (91 %). TFAA = trifluoroacetic anhydride, DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene.

At this stage in the synthesis several options were investigated towards the elimination of the aryl amine portion to re-introduce the unsaturation to the γ-lactone ring. After experimentation involving N-quaternisation, N-oxidation (followed by Cope elimination) and N-sulfonylation, we found that the optimum activation allowing facile elimination of the aryl amine was trifluoroacetamide formation. The eventual path to **5** actually involved "protection" of **35** as its trifluoroacetamide **36** using trifluoroacetic anhydride and Hünig's base followed by a three-step process to form the desired vinyl iodide. Thus hydrogenation of the benzyl ether over $Pd(OH)_2$ gave **37**, then Swern oxidation of the released hydroxyl group followed by one carbon homologation according to the Takai procedure[31] provided **38** as a 4:1 ratio of inseparable isomers in overall 64 % yield (four steps), favouring the *E*-geometry. Subsequent elimination of the trifluoroacetamide was effected using DBU at 0 °C, to afford **5** in 91 % yield with no epimerisation of the C-34 methyl substituent.

The final steps: The convergent assembly of muricatetrocin C from the three fragments **3**, **4** and **5** involves two key bond-forming events. The first coupling reaction between **3** and **4** forms the final C-16 stereogenic centre then, after manipulation to unmask a terminal alkyne, the second coupling event, to attach **5**, completes the carbon skeleton.

Treatment of the *gem*-dibromoalkene **15** with *n*-butyllithium in THF at $-78\,^{\circ}C$, followed by quenching of the resulting anion **39** with crude aldehyde **4**, proceeded in good yield to give the propargylic alcohols **40** and **41** (Scheme 9). Inspection of the crude ^{1}H NMR spectrum indicated that the reaction had proceeded with poor selectivity to afford **40** and **41** in a ratio of 1.8:1; tentatively assigned as favouring **40**, which is the product of Felkin–Anh control. Unfortunately the two epimers were inseparable at this stage. The yield of the coupling reaction was generally dependent on the quality of the crude aldehyde, and the poor diastereoselectivity was as expected based upon literature precedent.[32] Consequently an oxidation–reduction sequence was sought in order to establish the correct stereochemistry at C-16.

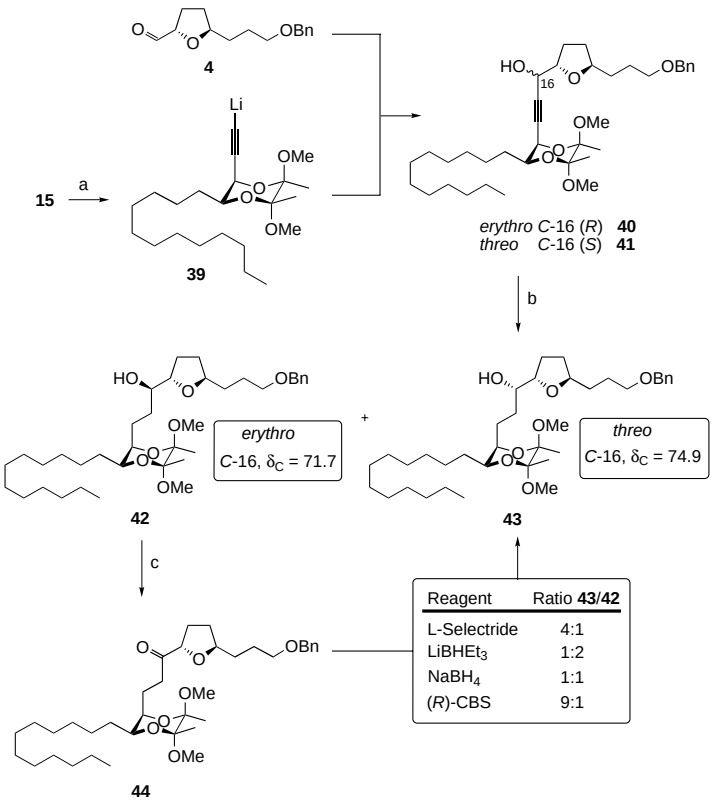
Reduction of the alkyne with hydrogen in the presence of Raney nickel proceeded smoothly to afford **42** and **43**, which were separable by column chromatography. Analysis of the ^{13}C NMR spectra of the two epimers, provided further evidence supporting the original stereochemical assignment of the major and minor products. By analogy with previous studies, the chemical shift of C-16 is dependent on the configuration of the adjacent THF ring, with the *erythro*-product **42**, having a lower chemical shift.[13a] In this instance, the difference between the two resonances was $\delta = 3.2$, which is typical for these systems.

After separation of the minor isomer **43**, the remaining material was oxidised using the Swern reagent to afford **44** in good yield. Several reducing agents were investigated in an attempt to develop a diastereoselective recycling protocol. L-Selectride in THF at $-100\,^{\circ}C$, was found to deliver the best selectivity, providing **43** and **42** in excellent yield as a 4:1 ratio favouring **43**; this result is consistent with those previously observed in the literature.[13b] Interestingly when Superhydride was used under the same conditions, the reduction favoured formation of the *erythro*-isomer (**43**/**42** 1:2), whereas sodium borohydride provided no diastereoselection in methanol at $0\,^{\circ}C$.

Using achiral reducing reagents, a 4:1 ratio favouring the desired *threo*-isomer was the best result obtained. Reduction using the enantiopure (*R*)-CBS reagent (CBS: Corey–Bakshi–Shibata) was also performed on the ketone **44**, which delivered a significantly higher ratio (**43**/**42** 9:1) of the C-16 epimers.[33] Furthermore, the stereochemical outcome, predicted using the mnemonic for reductions of this type, was in agreement with the stereochemistry previously assigned using the ^{13}C NMR chemical shift data, providing further proof of the configuration at C-16.

Protection of the free secondary alcohol was effected by treatment of **43** with TBSCl and imidazole in DMF in good yield to afford the silyl ether **45**, which then underwent debenzylation using hydrogen in the presence of catalytic palladium hydroxide to give **46** (Scheme 10). Oxidation to the corresponding aldehyde occurred in excellent yield using the Dess–Martin periodinane reagent in dichloromethane at $0\,^{\circ}C$.[34] Initial attempts at the one carbon homologation towards **47** focussed on the Corey–Fuchs procedure which had been successfully used earlier in the synthesis.[22] However, on reaction with in situ generated (dibromomethylene)triphenylphosphorane, complete decomposition of the starting material was observed.

This disappointing result may be attributed to competing acetal deprotection, which is known to be effected by the phosphorane reagent.[35] In addition, the small scale of the reaction may also have been a contributing factor. An alternative, well established procedure, for the conversion of aldehydes to terminal alkynes is the Colvin–Gilbert–Seyferth reagent, diethyl(diazomethyl)phosphonate.[36] In this case, owing to the greater nu-



Scheme 9. Coupling fragments **39** and **4**. a) *n*-BuLi, THF, $-78 \rightarrow 0\,^{\circ}C$, 30 min; $-78\,^{\circ}C$ then **4** (63% two steps; **40**/**41**, 1.8:1); b) Raney nickel, H_2, EtOH; rt, 60 min (**43** 18%, **42**+**43** 71%); c) DMSO, $(COCl)_2$, CH_2Cl_2, $-78\,^{\circ}C$; NEt_3, $-78 \rightarrow$ rt (80%).

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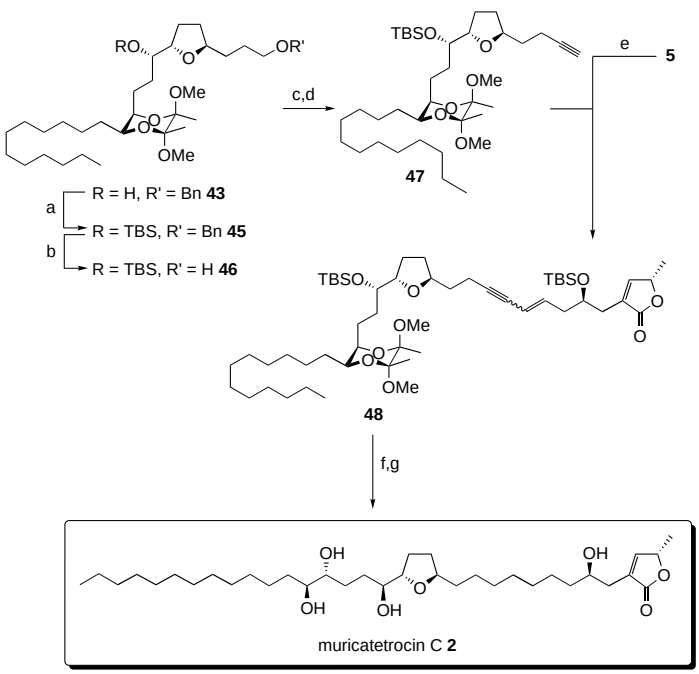

Scheme 10. Second coupling reaction and final steps. a) TBSCl, DMF, imidazole, 45 °C, 14 h (87 %); b) $Pd(OH)_2$ (20 mol %), H_2, EtOH; rt, 12 h (94 %); c) DMP, py, CH_2Cl_2, 0 °C → rt, 45 min (96 %); d) diethyl(diazomethyl)phosphonate, *t*BuOK, THF, −78 °C, 16 h; then rt, 4 h (76 %); e) $[(PPh_3)_2PdCl_2]$ (10 mol %), CuI (30 mol %), NEt_3, rt, 3 h (81 %); f) $[Rh(PPh_3)_3Cl]$, H_2, benzene/EtOH 1:1, rt, 11 h (76 %); g) TFA/H_2O 9:1, rt, 30 s; repeat (82 %). DMP = Dess–Martin periodinane, TFA = trifluoroacetic acid.

cleophilicity of the phosphonate anion, the reaction conditions are considerably milder and, perhaps more importantly, basic. Pleasingly, on reaction with the potassium anion of the phosphonate, the aldehyde afforded terminal alkyne **47** in good yield. This transformation completed the preparation of the coupling partner required for the Sonogashira reaction with fragment **5**.

According to the method of Hoye et al., alkyne **47** was added to a triethylamine solution of vinyl iodide **5**, $[Pd(PPh_3)_2Cl_2]$ and copper iodide at room temperature and stirred for two hours to afford, after purification by column chromatography, enyne **48** in good (81 %) yield.[20a] There was considerable literature precedent for the selective hydrogenation of the resulting enyne moiety in the presence of the α,β-unsaturated γ-lactone. According to this precedent, reduction of **48** with hydrogen in ethanol/benzene in the presence of Wilkinson's catalyst gave, after eleven hours, fully protected **2** in good (76 %) yield with no reduction of the butenolide portion.[20b] Both BDA and TBS groups are known to be acid labile, which was important in order to maintain the stereochemical integrity of the butenolide methyl substituent. Global deprotection was therefore achieved by treatment with aqueous trifluoroacetic acid for 30 seconds followed by concentration in vacuo. This process was repeated, then column chromatography afforded **2**, as a white amorphous solid in 82 % yield. The spectroscopic data for synthetic **2** (^{1}H NMR, ^{13}C NMR, IR, m.p. and specific rotation) were all in excellent agreement with those reported for the naturally occurring muricatetrocin C.[16]

Conclusion

In summary, the first total synthesis of **2** has been achieved by implementing new methods for the stereoselective preparation of each of the three coupling fragments. The route described here, has a longest linear sequence of 22 steps, and prepares muricatetrocin C in overall 2.8 % yield at average yield of 85 % per step. Thus our *anti*-diol building block, (*R′*,*R′*,*R*,*S*)-2,3-BDA-protected butane tetrol **6** has found further utility in total synthesis, the recently developed anomeric O–C rearrangement methodology has been used to install the 2,5-*trans*-disubstituted THF moiety **4** and a new approach to the hydroxy-butenolide terminus **5**, employing a highly diastereoselective HDA reaction, has been developed. Further studies aimed at expanding our synthetic approach to other members of this family of bioactive natural products are currently underway, and progress will be reported in due course.

Experimental Section

General: All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven-dried glassware, cooled under vacuum. Diethyl ether and tetrahydrofuran were distilled over sodium/benzophenone; dichloromethane, methanol, benzene and toluene were distilled over calcium hydride; pentane was distilled over sodium; and triethylamine from potassium hydroxide. Petroleum ether 40/60 was used for chromatography. All other solvents and reagents were used as supplied unless otherwise stated. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh) under pressure unless otherwise stated. High performance liquid chromatography (HPLC) was performed using a Waters Delta Prep machine using a multiwave detector set at 205 nm using silica gel as the stationary phase with the mobile phases and flow rate as described. Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with Merck Kieselgel 60F254, and visualised by UV irradiation (254 nm), or by staining with aqueous acidic ammonium molybdate, or aqueous acidic potassium permanganate solutions as appropriate. Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. Optical rotations were measured on an Optical Activity AA-1000 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g per 100 mL. Infrared spectra were obtained on Perkin Elmer 983G or FTIR 1620 spectrometers, from a thin film deposited onto a NaCl plate or mixed with KBr as a tablet. Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, Lensfield Road, Cambridge. Mass spectra and accurate mass data were obtained on a Micromass Platform LC-MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometer, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques at the Department of Chemistry, Lensfield Road, Cambridge. ^{1}H NMR spectra were recorded in $CDCl_3$, at ambient temperature on AM-200, AM-400, DPX-400 or DRX-600 Bruker spectrometers, at 200, 400 or 600 MHz, with residual protic solvent $CHCl_3$ as the internal reference ($\delta_H = 7.26$); Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows δ (multiplicity, coupling constant J, number of protons, assignment). ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on the same spectrometers at 50, 100 or 150 MHz, with the central peak of $CHCl_3$ as the internal reference ($\delta_C = 77.0$). DEPT135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid in the assignment of signals in the ^{1}H and ^{13}C NMR spectra; gradient NOE experiments were also performed in certain cases and their salient results are detailed in the text. Where a compound has been characterised as an inseparable mixture of diastereoisomers, the NMR data for each individual isomer has been reported as far as was discernible from the spectrum of the mixture. Where coincident coupling constants have

been observed in the NMR spectrum, the apparent multiplicity of the proton resonance concerned has been reported.

The *anti*-diol fragment

(2*S*,3*R*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-2-hydroxymethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane (10): A solution of **6** (3.86 g, 16.3 mmol) in THF (5 mL) was added dropwise through a syringe to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 720 mg, 18.0 mmol) in THF (10 mL) at 0 °C. After warming to rt over 30 min, pentane (15 mL) was added and the solution stirred for a further 30 min. *tert*-Butyldimethylchlorosilane (2.45 g, 16.3 mmol) in pentane (5 mL) was then added and the reaction mixture stirred for a further 40 min. The solution was then poured onto diethyl ether (250 mL), water (200 mL) was added and the organic phase separated. The aqueous layer was re-extracted with diethyl ether (100 mL) and the combined organic phase was washed with saturated NaCl solution (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (2:1+1% triethylamine) afforded mono-silylated diol **10** (4.13 g, 72%) as white cubes which were further recrystallised frm pentane/diethyl ether 10:1. M.p. 79 °C; R_f = 0.14 (petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D} = -118$ ($c = 1.00$ in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 4.35$ (t, $J = 9.9$ Hz, 1H; C*H*HOSi), 4.26–4.21 (m, 1H; C*H*CH_2OH), 3.73 (dt, $J = 9.9$, 2.4 Hz, 1H; C*H*CH_2OSi), 3.66 (dd, $J = 7.1$, 2.9 Hz, 2H; CH_2OH), 3.57 (dd, $J = 9.9$, 2.4 Hz, 1H; CH*H*OSi), 3.24 (s, 3H; OCH_3), 3.22 (s, 3H; OCH_3), 2.96 (t, $J = 7.1$ Hz, 1H; O*H*), 1.26 (s, 3H; CCH_3), 1.25 (s, 3H; CCH_3), 0.88 (s, 9H; C(CH_3)$_3$), 0.08 (s, 6H; Si(CH_3)$_2$); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 99.2$ (O*C*CH_3), 98.1 (O*C*CH_3), 72.8 (*C*HCH_2OSi), 67.9 (*C*HCH_2OH), 62.3 (*C*H_2OSi), 61.7 (*C*H_2OH), 49.3 (O*C*H_3), 47.9 (O*C*H_3), 25.8 (C(*C*H_3)$_3$), 18.2 (*C*(CH_3)$_3$), 18.1 (C*C*H_3), 17.9 (C*C*H_3), −5.5 (Si*C*H_3), −5.6 (Si*C*H_3); IR (KBr): $\nu_{max} = 3489$ (br, O-H), 2924, 2854 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{16}H_{34}O_6Si$: C 54.8, H 9.78; found: C 54.8, H 9.56.

(2*S*,3*R*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-5,6-dimethoxy-5,6-dimethyl-2-dodecane-[1,4]-dioxane (13)

1) Oxidation to the aldehyde: A solution of dimethyl sulfoxide (1.84 mL, 26.0 mmol) in dichloromethane (5 mL) was added to a vigorously stirred solution of oxalyl chloride (2.10 mL, 23.6 mmol) in dichloromethane (30 mL) at −78 °C. After 30 min, **10** (4.13 g, 11.8 mmol) in dichloromethane (15 mL) was added dropwise through a syringe and the temperature maintained at −78 °C for 1 h. Triethylamine (9.87 mL, 70.8 mmol) was then added and the solution allowed to warm to rt over 1 h. The reaction mixture was diluted with diethyl ether (300 mL), washed with phosphate buffer solution (pH 7.2, 150 mL) and saturated NaCl solution (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude oil solidified on standing to afford the aldehyde (4.1 g, >98%) which was used in the subsequent step without further purification. M.p. 49–50 °C; R_f = 0.41 (petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D} = -122$ ($c = 1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 9.49$ (s, 1H; C*H*O), 4.49 (d, $J = 4.0$ Hz, 1H; C*H*CHO), 4.30 (t, $J = 9.9$ Hz, 1H; C*H*HOSi), 4.10 (dt, $J = 9.9$, 4.0 Hz, 1H; C*H*CH_2OSi), 3.62 (dd, $J = 9.9$, 4.0 Hz, 1H; CH*H*OSi), 3.24 (s, 3H; OCH_3), 3.18 (s, 3H; OCH_3), 1.35 (s, 3H; CCH_3), 1.26 (s, 3H; CCH_3), 0.84 (s, 9H; C(CH_3)$_3$), 0.01 (s, 3H; Si*C*H_3), 0.01 (s, 3H; Si*C*H_3); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 195.6$ (*C*HO), 100.4 (O*C*CH_3), 98.5 (O*C*CH_3), 74.3 (*C*HCH_2OSi), 72.0 (*C*HCHO), 61.0 (*C*H_2OSi), 48.6 (O*C*H_3), 48.2 (O*C*H_3), 25.7 (C(*C*H_3)$_3$), 18.4 (C*C*H_3), 18.1 (*C*(CH_3)$_3$), 17.9 (C*C*H_3), −5.6 (Si*C*H_3), −5.7 (Si*C*H_3).

2) Wittig reaction: 1-Iodoundecane (6.20 g, 22.0 mmol), was added dropwise through a syringe to a solution of Ph_3P (5.48 g, 20.9 mmol) in toluene (6 mL). The reaction mixture was heated at reflux for 4 h and then cooled to rt. Concentration in vacuo afforded a pale yellow gum that was used without further purification (11.68 g, quant).

n-Butyllithium (1.6 M in hexanes, 12.6 mL, 20.2 mmol) was added dropwise through a syringe to the phosphonium salt (11.0 g, 20.2 mmol) in THF (30 mL) at 0 °C. After stirring at 0 °C for 30 min, the deep red solution was transferred dropwise via cannular to a solution of the aldehyde (prepared as above, 4.10 g, 11.8 mmol) in THF (15 mL) at −78 °C. The reaction mixture was warmed to 0 °C over 30 min, and phosphate buffer solution (pH 7.2, 10 mL) was then added. After dilution with diethyl ether (250 mL) the organic phase was separated, washed with saturated NaCl solution (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Filtration through a short pad of silica gel eluting with petroleum ether/diethyl ether (10:1) afforded the corresponding olefin (5.26 g, 92%), an oil, as an inseparable mixture of geometric isomers which was used without further purification in the subsequent step [*Z*/*E* 8:1; assigned by integration of the peaks at δ_H (major) = 4.94 (dd, $J = 8.8$, 4.2 Hz, 1H; C=CHC*H*) and δ_H (minor) = 4.49 (dd, $J = 8.8$, 4.2 Hz, 1H; C=CHC*H*)]. R_f = 0.45 (petroleum ether/diethyl ether 10:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 5.52 (dt, $J = 11.1$, 7.4 Hz, 1H; CH_2CH=C), 5.42 (dd, $J = 11.1$, 8.8 Hz, 1H; C=C*H*CH), 4.94 (dd, $J = 8.8$, 4.2 Hz, 1H; C=CHC*H*), 4.05 (dd, $J = 10.5$, 6.7 Hz, 1H; C*H*HOSi), 3.86 (dd, $J = 10.5$, 5.8 Hz, 1H; CH*H*OSi), 3.63–3.59 (m, 1H; C*H*CH_2OSi), 3.31 (s, 3H; OCH_3), 3.26 (s, 3H; OCH_3), 2.14–2.03 (m, 2H; CH_2C=C), 1.31–1.23 (m, 16H; (CH_2)$_8$), 1.29 (s, 3H; CCH_3), 1.28 (s, 3H; CCH_3), 0.88–0.85 (m, 12H; C(CH_3)$_3$, CH_2CH_3), 0.03 (s, 3H; SiCH_3), 0.02 (s, 3H; SiCH_3); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor, selected peaks) = 5.71 (dt, $J = 15.3$, 6.6 Hz, 1H; CH_2CH=C), 4.49 (dd, $J = 8.8$, 4.2 Hz, 1H; C=CHC*H*), 4.08–4.01 (m, 1H; C*H*HOSi), 3.75 (dd, $J = 10.4$, 4.9 Hz, 1H; CH*H*OSi), 3.27 (s, 3H; OCH_3), 3.22 (s, 3H; OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 133.4 (C=*C*CH), 125.7 (*C*=CCH), 99.7 (O*C*CH_3), 97.9 (O*C*CH_3), 75.3 (C=*C*CH), 64.9 (*C*HCH_2OSi), 62.1 (*C*H_2O-Si), 49.3 (O*C*H_3), 47.9 (O*C*H_3), 30.3 (*C*H_2C=C), 29.6 (5 × *C*H_2), 29.3 (*C*H_2), 28.1 (*C*H_2), 25.8 (C(*C*H_3)$_3$), 22.7 (*C*H_2), 18.5 (C*C*H_3), 18.4 (*C*(CH_3)$_3$), 18.1 (C*C*H_3), 14.1 (CH_2*C*H_3), −5.4 (Si*C*H_3), −5.4 (Si*C*H_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ (minor) = 133.8 (C=*C*CH), 125.8 (*C*=CCH), 99.6 (O*C*CH_3), 97.9 (O*C*CH_3), 75.6 (C=*C*CH), 70.0 (*C*HCH_2OSi), 62.2 (*C*H_2O-Si), 49.2 (O*C*H_3), 47.8 (O*C*H_3), 31.9 (*C*H_2C=C), 29.6 (5x*C*H_2), 29.3 (*C*H_2), 28.1 (*C*H_2), 25.8 (C(*C*H_3)$_3$), 22.7 (*C*H_2), 18.4 (C*C*H_3), 18.4 (*C*(CH_3)$_3$), 18.1 (C*C*H_3), 14.1 (CH_2*C*H_3), −5.4 (Si*C*H_3), −5.4 (Si*C*H_3).

3) Olefin reduction: A slurry of Raney nickel (50% in water, 6.0 g), was washed successively with 95% ethanol (3 × 15 mL) and absolute ethanol (3 × 15 mL). Absolute ethanol (8 mL) was then added and the suspension placed under a hydrogen atmosphere. The above olefin (1.20 g, 2.47 mmol) in absolute ethanol (5 mL) was added dropwise through a syringe and the reaction stirred vigorously for 30 min. Filtration through a short plug of silica eluting with diethyl ether, concentration in vacuo and purification by flash column chromatography (petroleum ether/diethyl ether 15:1) afforded silyl ether **13** (1.08 g, 90%) as an oil. R_f = 0.39 (petroleum ether/diethyl ether 10:1); $[\alpha]_{29}^{D} = -85$ ($c = 0.65$ in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): $\delta = 4.14$ (dd, $J = 10.2$, 8.2 Hz, 1H; C*H*HOSi), 4.06–4.04 (m, 1H; C*H*CH_2CH_2), 3.69 (dd, $J = 10.2$, 3.8 Hz, 1H; CH*H*OSi), 3.58 (dt, $J = 8.2$, 3.8 Hz, 1H; C*H*CH_2OSi), 3.26 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 1.52–1.43 (m, 2H; CH_2CH), 1.28–1.20 (m, 23H; (CH_2)$_{10}$, CCH_3), 1.27 (s, 3H; CCH_3), 0.88 (s, 9H; C(CH_3)$_3$), 0.88 (t, $J = 7.0$ Hz, 3H; CH_2CH_3), 0.04 (s, 6H; Si(CH_3)$_2$); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 99.5$ (O*C*CH_3), 98.0 (O*C*CH_3), 75.3 (*C*HCH_2OSi), 68.6 (CH_2*C*H), 62.3 (*C*H_2OSi), 49.3 (O*C*H_3), 47.7 (O*C*H_3), 31.9 (*C*H_2CH), 30.8 (*C*H_2), 29.6 (6 × *C*H_2), 29.3 (*C*H_2), 26.2 (*C*H_2), 25.8 (C(*C*H_3)$_3$), 22.7 (*C*H_2), 18.3 (C*C*H_3), 18.1 (*C*(CH_3)$_3$), 18.1 (C*C*H_3), 14.1 (CH_2*C*H_3), −5.4 (Si*C*H_3), −5.4 (Si*C*H_3); IR (film): ν_{max} = 2925, 2854 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{27}H_{56}O_5Si$: C 66.3, H 11.55; found: C 66.5, H 11.51.

(2*S*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-hydroxymethyl-2-dodecane-[1,4]-dioxane (14): TBAF (1.0 M in THF, 4.40 mL, 4.40 mmol) was added in one portion to a solution of **13** (1.08 g, 2.21 mmol) in THF (4.4 mL) at rt and the reaction stirred for 2 h. Removal of the volatiles in vacuo and filtration through a pad of silica, eluting with diethyl ether afforded primary alcohol **14** (810 mg, 99%) as an oil. R_f = 0.12 (petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D} = -104$ ($c = 1.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 4.05$ (dt, $J = 8.9$, 4.3 Hz, 1H; CH_2CH_2CH), 3.80 (br s, 2H; CH_2OH), 3.67 (br s, 1H; O*H*), 3.55–3.53 (m, 1H; C*H*CH_2OH), 3.35 (s, 3H; OCH_3), 3.21 (s, 3H; OCH_3), 1.78–1.70 (m, 1H; CH_2C*H*H), 1.56–1.44 (m, 2H; CH_2), 1.31 (s, 3H; CCH_3), 1.29–1.20 (m, 19H; (CH_2)$_9$, CH*H*), 1.26 (s, 3H; CCH_3), 0.85 (t, $J = 6.8$ Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 99.3$ (O*C*CH_3), 97.8 (O*C*CH_3), 74.2 (*C*HCH_2OH), 68.2 (CH_2CH_2*C*H), 63.1 (*C*H_2OH), 49.0 (O*C*H_3), 47.7 (O*C*H_3), 31.9 (CH_2*C*H_2CH), 30.2 (*C*H_2), 29.6 (6 × *C*H_2), 29.3 (*C*H_2), 26.1 (*C*H_2), 22.6 (*C*H_2), 18.2 (C*C*H_3), 18.0 (C*C*H_3), 14.0 (CH_2*C*H_3); IR (film): ν_{max} = 3480 (br, O-H), 2924, 2853 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{21}H_{42}O_5$: C 67.3, H 11.30; found: C 67.2, H 11.07.

(2*S*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-2-dodecane-3-(2′,2′-*gem*-dibromo)ethenyl-[1,4]-dioxane (15)

1) Oxidation to the aldehyde: A solution of dimethyl sulfoxide (0.34 mL, 4.77 mmol) in dichloromethane (5 mL) was added dropwise through a syringe to a vigorously stirred solution of oxalyl chloride (0.38 mL,

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4.34 mmol) in dichloromethane (10 mL) at −78 °C. After stirring for 30 min, **14** (810 mg, 2.17 mmol) in dichloromethane (5 mL) was added dropwise through a syringe. After stirring at −78 °C for 1 h, triethylamine (1.80 mL, 13.0 mmol) was added dropwise through a syringe and the solution warmed to rt over 1 h. The reaction mixture was diluted with diethyl ether (100 mL) and washed with phosphate buffer solution (pH 7.2, 50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. This afforded the aldehyde (810 mg, >98%), an oil, which was used with no further purification. $R_f = 0.50$ (petroleum ether/diethyl ether 2:1); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 9.96$ (d, $J = 3.0$ Hz, 1H; C*H*O), 4.11–4.07 (m, 1H; CH_2CH), 3.56 (t, $J = 3.0$ Hz, 1H; C*H*CHO), 3.26 (s, 3H; OCH_3), 3.17 (s, 3H; OCH_3), 1.72–1.68 (m, 1H; C*H*H), 1.53–1.41 (m, 2H; CH_2), 1.33 (s, 3H; CCH_3), 1.31 (s, 3H; CCH_3), 1.29–1.21 (m, 19H; $(CH_2)_9$, CH*H*), 0.87 (t, $J = 6.8$, 3H; CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 200.7$ (*C*HO), 99.7 ($OCCH_3$), 98.8 ($OCCH_3$), 76.1 (*C*HCHO), 67.3 (CH_2CH), 49.1 (OCH_3), 47.9 (OCH_3), 31.9 (CH_2CH), 29.6 ($7 \times CH_2$), 29.4 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 18.0 (CCH_3), 17.4 (CCH_3), 14.1 (CH_2CH_3).

2) Homologation to the *gem*-dibromo olefin: Ph_3P (2.28 g, 8.68 mmol) was added portionwise to a solution of CBr_4 (1.44 g, 4.34 mmol) in dichloromethane (10 mL) at 0 °C. After 30 min, the above aldehyde (810 mg, 2.17 mmol), as a solution in dichloromethane (6 mL), was added dropwise through a syringe. After stirring at 0 °C for a further 30 min the reaction mixture was poured onto petroleum ether (100 mL) and the yellow precipitate was removed by filtration under reduced pressure. Concentration in vacuo and purification by flash column chromatography eluting with petroleum ether/diethyl ether (15:1) afforded *gem*-dibromo olefin **15** (0.98 g, 88%) as an oil. $R_f = 0.36$ (petroleum ether/diethyl ether 15:1); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 7.05$ (d, $J = 9.4$ Hz, 1H; C*H*=CBr_2), 4.16 (dd, $J = 9.4$, 3.6 Hz, 1H; C*H*CH=CBr_2), 4.07–4.03 (m, 1H; C*H*CH_2), 3.24 (s, 3H; OCH_3), 3.19 (s, 3H; OCH_3), 1.48–1.37 (m, 2H; CH_2), 1.29 (s, 3H; CCH_3), 1.29–1.21 (m, 23H; $(CH_2)_{10}$, CCH_3), 0.88 (t, $J = 6.7$ Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 136.4$ (*C*HCBr_2), 99.6 ($OCCH_3$), 98.5 ($OCCH_3$), 93.1 (CH=*C*Br_2), 73.4 (*C*HCH=CBr_2), 67.9 (*C*HCH_2), 48.4 (OCH_3), 47.8 (OCH_3), 31.9 (*C*H_2CH), 30.2 (CH_2), 29.6 ($6 \times CH_2$), 29.3 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 18.0 (CCH_3), 17.9 (CCH_3), 14.1 (CH_2CH_3); IR (film): $\nu_{max} = 2925$, 2853 (C-H), 1612 cm^{-1} (C=C); ES-MS: *m*/*z* (%): calcd for $C_{22}H_{40}O_4{}^{79}Br_2$: 526.1293; found: 526.1326.

The central fragment

(2*S*)-1-(*tert*-Butyldiphenylsilyloxy)prop-2-enoxide (16):[37] Triethylamine (16.8 mL, 121 mmol), TBDPSCl (21.5 mL, 82.9 mmol) and dimethylaminopyridine (2.80 g, 22.6 mmol) were added to a stirred solution of (*R*)-(+)-glycidol (5.60 g, 75.3 mmol) in dichloromethane (150 mL), and the reaction mixture was stirred for 24 h. HCl solution (1.5 N, 100 mL) was added and the organic phase separated. The aqueous layer was re-extracted with dichloromethane (2×100 mL), and the combined organic phase was washed with saturated sodium bicarbonate solution (150 mL), saturated NaCl solution (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (20:1 → 10:1) gave the TBDPS ether **16** (20.0 g, 85%) as an oil. $R_f = 0.34$ (petroleum ether/diethyl ether 10:1); $[\alpha]_{29}^{D} = -2.1$ ($c = 1.8$ in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 7.75-7.73$ (m, 4H; Ph), 7.49–7.41 (m, 6H; Ph), 3.90 (dd, $J = 11.8$, 3.1 Hz, 1H; C*H*HOSi), 3.76 (dd, $J = 11.8$, 4.7 Hz, 1H; CH*H*OSi), 3.18–3.14 (m, 1H; C*H*CH_2OSi), 2.77 (t, $J = 4.3$ Hz, 1H; C*H*HCHCH_2OSi), 2.66–2.63 (m, 1H; CH*H*CHCH_2O-Si), 1.12 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 135.7$ (Ph), 135.6 (Ph), 133.3 (*ipso C*-Si), 129.8 (Ph), 127.8 (Ph), 127.7 (Ph), 64.3 (CH_2CHCH_2OSi), 52.3 ($CHCH_2OSi$), 44.5 (CH_2OSi), 26.8 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); elemental analysis calcd (%) for $C_{19}H_{24}O_2Si$: C 73.0, H 7.74; found: C 72.9, H 7.67.

(2*R*/*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-tetrahydrofuran-2-ol (17)[38]

1) Allylation of 16: Dilithium tetrachlorocuprate (0.10 M in THF, 15 mL, 1.5 mmol) followed by allyl magnesium bromide (1.0 M in THF, 76.8 mL, 76.8 mmol) was added at −30 °C to a stirred solution of **16** (20.0 g, 64.0 mmol) in THF (100 mL). After 15 min at −30 °C, saturated ammonium chloride solution (100 mL) was added and the suspension warmed to rt. Water (100 mL) was then added and the reaction mixture extracted with diethyl ether (2×100 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by flash column chromatography, eluting with petroleum ether/diethyl ether (6:1) gave the secondary alcohol (20.1 g, 89%) as an oil. $R_f = 0.27$ (petroleum ether/diethyl ether 4:1); $[\alpha]_{29}^{D} = -7.8$ ($c = 2.3$ in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): $\delta = 7.73-7.71$ (m, 4H; Ph), 7.47–7.41 (m, 6H; Ph), 5.89–5.78 (m, 1H; C*H*=CH_2), 5.06–4.97 (m, 2H; CH=C*H*$_2$), 3.82–3.75 (m, 1H; C*H*OH), 3.72 (dd, $J = 10.1$, 3.4 Hz, 1H; C*H*HOSi), 3.56 (dd, $J = 10.1$, 7.3 Hz, 1H; CH*H*OSi), 2.57 (d, $J = 3.7$ Hz, 1H; O*H*), 2.27–2.09 (m, 2H; CH_2CH=CH_2), 1.64–1.47 (m, 2H; CH_2CHOH), 1.13 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 138.3$ (Ph), 135.6 (Ph), 133.2 (*ipso C*-Si), 129.9 (*C*H=CH_2), 127.8 (Ph), 114.8 (CH=*C*H_2), 71.4 (*C*HOH), 68.0 (CH_2OSi), 32.0 (CH_2), 29.8 (CH_2), 26.9 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$); IR (film): $\nu_{max} = 3430$ (br, OH), 3072, 2931, 2858 (C-H), 1640 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{22}H_{30}O_2Si$: C 74.5, H 8.53; found: C 74.6, H 8.48; EI-MS: *m*/*z* (%): 337.2 (33) $[M - OH]^+$, 297.1 (52) $[M - C_4H_9]^+$, 199.1 (100) $[M - 2 \times Ph]^+$.

2) Ozonolysis: Sodium bicarbonate (1.50 g) was added to a stirred solution of the above secondary alcohol (10.1 g, 28.7 mmol) in dichloromethane (250 mL) at −78 °C. O_3 (2 L s^{-1}) was then bubbled through until the reaction mixture became light blue (about 20 min). Ph_3P (9.00 g, 34.4 mmol) was added to the reaction mixture, which was warmed to rt and stirred for 14 h; at which point the solvent was removed in vacuo. Purification by flash column chromatography, eluting with petroleum ether/diethyl ether (10:1 → 2:1) afforded lactol **17** (9.47 g, 93%), an oil, as an inseparable, 3:2 mixture of anomers [assigned by integration of the peaks at δ_H (major) = 5.59 (br t, $J = 3.2$ Hz, 1H; *H*-2) and δ_H (minor) = 5.48 (dd, $J = 6.6$, 3.6 Hz, 1H; *H*-2)]. $R_f = 0.25$ (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 7.73–7.69 (m, 4H; Ph), 7.45–7.37 (m, 6H; Ph), 5.59 (br t, $J = 3.2$ Hz, 1H; *H*-2), 4.41–4.35 (m, 1H; *H*-5), 3.66 (d, $J = 4.7$ Hz, 2H; CH_2OSi), 3.27 (d, $J = 2.3$ Hz, 1H; O*H*), 2.20–1.70 (m, 4H; H_2-3, H_2-4), 1.08 (s, 9H; $C(CH_3)_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor) = 7.73–7.69 (m, 4H; Ph), 7.45–7.37 (m, 6H; Ph), 5.48 (dd, $J = 6.6$, 3.6 Hz, 1H; *H*-2), 4.27–4.22 (m, 1H; *H*-5), 3.84 (dd, $J = 10.8$, 3.6 Hz, 1H; C*H*HOSi), 3.63 (dd, $J = 10.8$, 3.8 Hz, 1H; CH*H*OSi), 3.53 (d, $J = 6.6$ Hz, 1H; O*H*), 2.20–1.70 (m, 4H; H_2-3, H_2-4), 1.11 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 135.6 (Ph), 133.6 (*ipso C*-Si), 129.6 (Ph), 127.7 (Ph), 99.0 (*C*-2), 79.0 (*C*-5), 66.2 (CH_2OSi), 32.8 (*C*-3), 26.9 ($C(CH_3)_3$), 25.4 (*C*-4), 19.3 ($C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (minor) = 135.7 (Ph), 132.9 (*ipso C*-Si), 129.8 (Ph), 127.8 (Ph), 98.6 (*C*-2), 80.3 (*C*-5), 66.5 (CH_2OSi), 34.6 (*C*-3), 26.8 ($C(CH_3)_3$), 24.1 (*C*-4), 19.2 ($C(CH_3)_3$); IR (film): ν_{max} (mixture) = 3404 (br, OH), 3070, 2930, 2857 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{21}H_{28}O_3Si$: C 70.7, H 7.92; found: C 70.4, H 7.81; EI-MS: *m*/*z* (%): 339.3 (77) $[M - OH]^+$, 117.1 (100) $[M - C_{16}H_{19}Si]^+$.

(2*R*/*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-2-(prop-2-yne-1-oxy)-tetrahydrofuran (18): Amberlyst A-15 (100 mg) was added to a stirred solution of **17** (7.20 g, 20.2 mmol) and prop-2-yn-1-ol (30 mL, 0.50 mol) in benzene (100 mL) in a round bottomed flask fitted with a distillation head and condenser. The reaction mixture was heated to 80 °C and 20 mL of benzene/water azeotrope removed through distillation. The reaction was then cooled to rt, filtered and the volatiles removed in vacuo. Filtration through a short pad of silica gel, eluting with petroleum ether/diethyl ether (6:1) yielded propargylic ether **18** (7.20 g, 91%) an oil, as an inseparable, 3:2 mixture of anomers [assigned by integration of the peaks at δ_H (major) = 5.34 (d, $J = 4.2$ Hz, 1H; *H*-2) and δ_H (minor) = 5.30 (d, $J = 3.7$ Hz, 1H; *H*-2)]. $R_f = 0.60$ (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 7.72–7.70 (m, 4H; Ph), 7.46–7.38 (m, 6H; Ph), 5.34 (d, $J = 4.2$ Hz, 1H; *H*-2), 4.27–4.22 (m, 3H; C*H*$_2$OCH, *H*-5), 3.70–3.67 (m, 2H; C*H*$_2$OSi), 2.41 (t, $J = 2.3$ Hz, 1H; C≡C*H*), 2.13–1.75 (m, 4H; H_2-3, H_2-4), 1.09 (s, 9H; $C(CH_3)_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor) = 7.72–7.70 (m, 4H; Ph), 7.46–7.38 (m, 6H; Ph), 5.30 (d, $J = 3.7$ Hz, 1H; *H*-2), 4.27–4.22 (m, 1H; *H*-5), 4.16 (d, $J = 2.3$ Hz, 2H; CH_2OCH), 3.70–3.67 (m, 2H; CH_2OSi), 2.37 (t, $J = 2.3$ Hz, 1H; C≡C*H*), 2.13–1.75 (m, 4H; H_2-3, H_2-4), 1.10 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 135.7 (Ph), 134.0 (*ipso C*-Si), 129.6 (Ph), 127.7 (Ph), 102.8 (*C*-2), 80.4 (*C*≡CH), 79.0 (*C*-5), 73.7 (C≡*C*H), 66.0 (*C*H$_2$OCH), 53.8 (CH_2OSi), 32.0 (*C*-3), 26.8 ($C(CH_3)_3$), 25.3 (*C*-4), 19.3 ($C(CH_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (minor) = 135.6 (Ph), 134.0 (*ipso C*-Si), 129.6 (Ph), 127.6 (Ph), 102.3 (*C*-2), 81.3 (*C*-5), 80.3 (*C*≡CH), 73.7 (C≡*C*H), 67.5 (CH_2OCH), 53.5 (CH_2OSi), 32.8 (*C*-3), 26.8 ($C(CH_3)_3$), 25.9 (*C*-4), 19.3 ($C(CH_3)_3$); IR (film): $\nu_{max} = 3293$ (C≡C-H), 3070, 2930, 2857 (C-H), 2118 (C≡C), 1589 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{24}H_{30}O_3Si$: C

73.1, H 7.66; found: C 73.2, H 7.75; EI-MS: *m/z* (%): 281.1 (100) [*M* − (C_4H_9+C_3H_3O)]$^+$, 225.1 (58), 199.1 (55).

(2*R*/*S*,5*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(1-hydroxyprop-2-ynyl) tetrahydrofuran 19 (2*S*) and 20 (2*R*): *n*-Butyllithium (1.6 M in hexanes, 2.50 mL, 4.00 mmol) was added dropwise through a syringe to a solution of **18** (1.45 g, 3.7 mmol) in THF (2.5 mL) at −78 °C. The solution was stirred at −78 °C for 30 min then tributyltinchloride (1.00 mL, 3.90 mmol) was added dropwise through a syringe and the reaction warmed to rt. Following dilution with diethyl ether (50 mL), washing with water (30 mL) and saturated NaCl solution (30 mL), drying ($MgSO_4$) and evaporation of volatiles in vacuo gave the stannylated material **7** as a viscous oil, which was used without purification in the next step.

Boron trifluoride etherate (1.40 mL, 11.0 mmol) was added dropwise through a syringe to a solution of **7** (2.64 g) in dichloromethane (1 mL) with vigorous stirring at −10 °C. The reaction was stirred for 10 min at −10 °C and then quenched by the addition of NaOH solution (10%, 2 mL). Following dilution with dichloromethane (30 mL), the organic phase was separated, washed with saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (20:1 then 2:1 → 1:2). The oil resulting from evaporation of the fractions containing a mixture of *cis* and *trans* isomers was further purified by flash column chromatography eluting with petroleum ether/diethyl ether (20:1 then 1:1) to give **19** and **20** (1.16 g, 85%) as an oil, as an inseparable mixture of *trans* and *cis* isomers [**19**/**20**, 5.5:1; assigned by integration of the peaks at δ_H (major) = 4.74 (t, J = 6.2 Hz, 1H; *H*-5) and δ_H (minor) = 4.64 – 4.61 (m, 1H; *H*-5)]. R_f = 0.18 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 7.72 – 7.67 (m, 4H; Ph), 7.45 – 7.37 (m, 6H; Ph), 4.74 (t, J = 6.2 Hz, 1H; *H*-5), 4.31 (dd, J = 5.9, 1.3 Hz, 2H; CH_2OSi), 4.28 – 4.23 (m, 1H; *H*-2), 3.71 – 3.63 (m, 2H; C≡CCH_2), 2.27 – 1.88 (m, 4H; H_2-3, H_2-4), 1.06 (s, 9H; C(CH_3)$_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor) = 7.72 – 7.67 (m, 4H; Ph), 7.45 – 7.37 (m, 6H; Ph), 4.64 – 4.61 (m, 1H; *H*-5), 4.21 (dd, J = 6.1, 1.3 Hz, 2H; CH_2OSi), 4.10 (m, 1H; *H*-2), 3.79 (dd, J = 10.5, 4.7 Hz, 1H; C≡CC*H*H), 3.71 – 3.63 (m, 1H; C≡CCH*H*), 2.27 – 1.88 (m, 4H; H_2-3, H_2-4), 1.07 (s, 9H; C(CH_3)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 135.7 (Ph), 133.7 (*ipso C*-Si), 129.6 (Ph), 127.7 (Ph), 85.8 (CHC≡C), 82.7 (CHC≡*C*), 79.4 (*C*-2), 68.6 (*C*-5), 66.0 (*C*H$_2$OSi), 51.1 (C≡C*C*H$_2$), 33.4 (*C*-4), 27.4 (*C*-3), 26.8 (C(*C*H$_3$)$_3$), 19.2 (*C*(CH$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (minor) = 135.6 (Ph), 133.8 (*ipso C*-Si), 129.6 (Ph), 127.7 (Ph), 85.8 (CHC≡C), 82.7 (CHC≡*C*), 80.3 (*C*-2), 68.6 (*C*-5), 66.5 (*C*H$_2$OSi), 51.2 (C≡CCH_2), 33.1 (*C*-4), 28.1 (*C*-3), 26.8 (C(*C*H$_3$)$_3$), 19.2 (*C*(CH$_3$)$_3$); IR (film): ν_{max} = 3406 (br, O-H), 3070, 2930, 2857 (C-H), 1589 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{24}H_{30}O_3Si$: C 73.1, H 7.66; found: C 73.5, H 7.63; FAB-MS: *m/z* (%): calcd for $C_{24}H_{30}O_3SiNa$: 417.1862; found: 417.1848; EI-MS: *m/z* (%): 338 (12) [*M* − C_4H_9]$^+$, 199 (66), 135 (100).

(2*S*,5*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(1-benzyloxyprop-2-ynyl)-tetrahydrofuran (21): KHMDS (0.5 M in toluene, 6.50 mL, 3.20 mmol) was added dropwise through a syringe to a solution of **19** and **20** (1.16 g, 2.90 mmol) in THF (6.5 mL) at −78 °C. The solution was stirred at −78 °C for 30 min and then benzyl bromide (1.0 mL, 8.8 mmol) was added dropwise through a syringe. The reaction was then allowed to warm to rt and stirred for a further 2 h. The reaction mixture was diluted with diethyl ether (100 mL), then quenched by the addition of water (5 mL). The organic phase was separated, washed with aqueous HCl solution (3 N, 2 × 30 mL) and saturated NaCl solution (30 mL), dried ($MgSO_4$) and the volatiles removed in vacuo. The resulting mixture of 5.5:1 diastereoisomers [assigned by integration of the peaks at δ_H (major) = 4.81 – 4.79 (m, 1H; *H*-5) and δ_H (minor) = 4.70 – 4.68 (m, 1H; *H*-5) in the crude ^{1}H NMR] could be separated by MPLC chromatography eluting with petroleum ether/diethyl ether (9:1) to afford **21** (1.11 g, 78%) and the minor *cis*-isomer **22** (200 mg, 14%). R_f (major) = 0.25 (petroleum ether/diethyl ether 4:1); R_f (minor) = 0.20 (petroleum ether/diethyl ether 4:1); $[\alpha]_{29}^{D}$ (major) = −17.3 (c = 0.95 in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): δ (major) = 7.73 – 7.70 (m, 4H; Ph), 7.46 – 7.36 (m, 10H; Ph), 7.33 – 7.31 (m, 1H; Ph), 4.81 – 4.79 (m, 1H; *H*-5), 4.64 (d, J = 11.9 Hz, 1H; PhC*H*H), 4.62 (d, J = 11.9 Hz, 1H; PhCH*H*), 4.32 – 4.28 (m, 1H; *H*-2), 4.25 (d, J = 1.5 Hz, 2H; C≡CCH_2), 3.73 (dd, J = 10.8, 4.7 Hz, 1H; C*H*HOSi), 3.70 (dd, J = 10.8, 4.2 Hz, 1H; CH*H*OSi), 2.29 – 2.24 (m, 1H; *H*-4), 2.19 – 2.14 (m, 1H; *H*-3), 2.06 – 2.01 (m, 1H; *H*-4), 1.99 – 1.93 (m, 1H; *H*-3), 1.10 (s, 9H; C(CH_3)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 137.5 (*ipso C*-C), 135.6 (Ph), 133.8 (*ipso C*-Si), 129.7 (Ph), 128.4 (Ph), 128.1 (Ph), 127.8 (Ph), 127.7 (Ph), 86.6 (CH*C*≡C), 80.4 (CHC≡*C*), 79.3 (*C*-2), 71.6 (Ph*C*H$_2$), 68.7 (*C*-5), 66.0 (*C*H$_2$OSi), 57.5 (C≡C*C*H$_2$), 33.5 (*C*-4), 27.4 (*C*-3), 26.8 (C(*C*H$_3$)$_3$), 19.3 (*C*(CH$_3$)$_3$); IR (film): ν_{max} (major) = 3070, 2929, 2856 (C-H), 1589 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{31}H_{36}O_3Si$: C 76.8, H 7.49; found (major): C 76.5, H 7.48; LREI-MS (major): *m/z*: 507 (52) [*M*+Na]$^+$, 427 (30) [*M* − C_4H_9]$^+$, 281 (100).

(2*S*,5*S*)-2-(Hydroxymethyl)-5-(1-benzyloxyprop-2-ynyl)tetrahydrofuran (23): TBAF (1.0 M in THF, 5.20 mL, 5.20 mmol) was added to a solution of **21** (500 mg, 1.03 mmol) in THF (5 mL) at rt and the reaction stirred for 3 h. Subsequent removal of all volatiles in vacuo followed by filtration through a small pad of silica eluting with diethyl ether afforded primary alcohol **23** (242 mg, 95%) as an oil. R_f = 0.33 (diethyl ether); $[\alpha]_{29}^{D}$ = −13.4 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.35 – 7.26 (m, 5H; Ph), 4.76 (br t, J = 6.0 Hz, 1H; *H*-5), 4.58 (s, 2H; PhCH_2), 4.27 – 4.23 (m, 1H; *H*-2), 4.21 (d, J = 1.2 Hz, 2H; C≡CCH_2), 3.70 (dd, J = 11.7, 3.2 Hz, 1H; C*H*HOSi), 3.51 (dd, J = 11.7, 5.5 Hz, 1H; CH*H*OSi), 2.27 – 2.18 (m, 1H; *H*-3), 2.16 – 1.99 (m, *H*-3, 3H; *H*-4, O*H*), 1.79 – 1.69 (m, 1H; *H*-4); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 137.42 (*ipso C*-C), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 86.1 (CH*C*≡C), 80.8 (CHC≡*C*), 79.4 (*C*-2), 71.6 (*C*H$_2$Ph), 68.6 (*C*-5), 64.5 (*C*H$_2$OH), 57.4 (C≡C*C*H$_2$), 33.6 (*C*-4), 26.8 (*C*-3); elemental analysis calcd (%) for $C_{15}H_{18}O_3$: C 73.1, H 7.37; found: C 72.6, H 7.39; FAB-MS: *m/z*: calcd for $C_{15}H_{18}O_3Na$: 269.1154; found: 269.1161; EI-MS: *m/z*: 269.0 (100) [*M*+Na]$^+$, 154 (55) [*M* − C_7H_7]$^+$.

(2*S*,5*R*)-2-(Carboxymethyl)-5-(1-benzyloxypropyl)tetrahydrofuran (4)

1) Saturation of the alkyne 23: A slurry of Raney nickel (1.2 g, 50% in H_2O), was washed successively with 95% ethanol (3 × 10 mL) and absolute ethanol (3 × 10 mL). Absolute ethanol (5 mL) was then added and the suspension was placed under a hydrogen atmosphere. **23** (328 mg, 1.33 mmol) was added in one portion through a syringe in absolute ethanol (5 mL) and the solution stirred vigorously for 30 min. Filtration through a pad of silica eluting with diethyl ether, concentration in vacuo and purification by flash column chromatography (petroleum ether/diethyl ether 1:2) gave the primary alcohol (230 mg, 70%) as an oil. R_f = 0.29 (diethyl ether); $[\alpha]_{29}^{D}$ = −8.6 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.36 – 7.32 (m, 4H; Ph), 7.31 – 7.26 (m, 1H; Ph), 4.51 (s, 2H; CH_2Ph), 4.13 – 4.07 (m, 1H; *H*-2), 4.01 – 3.93 (m, 1H; *H*-5), 3.64 – 3.60 (m, 1H; C*H*HOH), 3.53 – 3.46 (m, 3H; CH*H*OH, CH_2OBn), 2.07 – 1.93 (m, 3H; *H*-3, *H*-4, O*H*), 1.74 – 1.51 (m, 6H; CH_2CH_2CH$_2$OBn, *H*-3, *H*-4); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.6 (*ipso C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 79.2 (*C*-2), 78.8 (*C*-5), 72.9 (*C*H$_2$Ph), 70.3 (*C*H$_2$OBn), 65.1 (*C*H$_2$OH), 32.3 (*C*-3), 32.0 (*C*-4), 27.5 (*C*H$_2$), 26.5 (*C*H$_2$); IR (film): ν_{max} = 3427 (br, O-H), 3070, 2933, 2867 (C-H), 1589 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{15}H_{22}O_3$: C 72.0, H 8.86; found: C 71.6, H 8.98; EI-MS: *m/z*: calcd for $C_{15}H_{22}O_3$: 250.1569; found: 250.1556.

2) Swern oxidation: A solution of DMSO (0.22 mL, 3.10 mmol) in dichloromethane (6 mL) was added dropwise through a syringe to a vigorously stirred solution of oxalyl chloride (0.24 mL, 2.80 mmol) in dichloromethane at −78 °C. After 30 min, a solution of the above primary alcohol (350 mg, 1.4 mmol) in dichloromethane was added dropwise through a syringe and the reaction mixture stirred at −78 °C for a further 30 min. Triethylamine (1.20 mL, 8.40 mmol) was added, then the reaction mixture was stirred at −78 °C for 20 min before warming to rt over 30 min. The reaction mixture was poured onto phosphate buffer solution (10 mL, pH 7.2) and diethyl ether (25 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford aldehyde **4** as a yellow oil which was used without further purification in the coupling step with fragment **3**. R_f = 0.11 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.65 (d, J = 1.6 Hz, 1H; C*H*O), 7.37 – 7.31 (m, 4H; Ph), 7.30 – 7.27 (m, 1H; Ph), 4.51 (s, 2H; PhCH_2), 4.31 (td, J = 8.3, 1.6 Hz, 1H; *H*-2), 4.07 – 4.01 (m, 1H; *H*-5), 3.56 – 3.47 (m, 2H; CH_2OBn), 2.22 – 2.15 (m, 1H; *H*-3), 2.06 – 1.91 (m, 2H; *H*-3, *H*-4), 1.79 – 1.54 (m, 5H; *H*-4, CH_2CH_2); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 203.1 (*C*HO), 138.6 (*ipso C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 82.4 (*C*-2), 80.9 (*C*-5), 72.9 (*C*H$_2$Ph), 70.1 (*C*H$_2$OBn), 32.0 (*C*-3), 31.1 (*C*-4), 27.2 (*C*H$_2$), 26.4 (*C*H$_2$).

The butenolide terminus

1-Benzyloxy-butan-4-ol (27): A solution of 1,4-butanediol (3.90 mL, 44.0 mmol) in DMF (8 mL) was added to a suspension of sodium hydride (880 mg, 22.0 mmol) in DMF (25 mL) at 0 °C. After 1 h at 0 °C, benzylbromide (2.60 mL, 22.0 mmol) was added dropwise via syringe. The solution was stirred for a further 15 min then diluted with diethyl ether (250 mL) and poured onto a saturated ammonium chloride solution

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(100 mL). The organic phase was separated and washed with water (2 × 100 mL), saturated NaCl solution (80 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purified by flash column chromatography eluting with petroleum ether/diethyl ether (3:1 → 1:1) afforded alcohol **27** (6.50 g, 82 %) as an oil. $R_f = 0.13$ (petroleum ether/diethyl ether 1:1); ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 7.35-7.31$ (m, 5H; Ph), 4.52 (s, 2H; PhCH_2), 3.52 (t, $J = 4.2$ Hz, 2H; PhCH$_2$OCH_2), 3.64–3.61 (m, 2H; CH_2OH), 2.46 (br s, 1H; O*H*), 1.72–1.65 (m, 4H; CH_2CH_2CH$_2$OH); ^{13}C NMR (50 MHz; $CDCl_3$): $\delta = 138.3$ (*ipso C*-C), 128.3 (Ph), 127.6 (Ph), 127.6 (Ph), 72.9 (PhCH_2), 70.3 (CH_2OH), 62.2 (CH_2OCH$_2$Ph), 29.7 (CH_2), 26.4 (CH_2); IR (film): $\nu_{max} =$ 3381 cm^{-1} (br, O-H); elemental analysis calcd (%) for $C_{11}H_{16}O_2$: C 73.3, H 8.90; found: C 72.9, H 8.99.

(*E*)-*tert*-Butyl-6-benzyloxy-hex-2-enoate (28): A solution of dimethyl sulfoxide (25.6 mL, 361 mmol) in dichloromethane (140 mL) was added dropwise through a syringe over a period of 30 min to a vigorously stirred solution of oxalyl chloride (14.9 mL, 171 mmol) in dichloromethane (470 mL) at −78 °C. The resulting mixture was stirrred for a further 30 min at −78 °C, then a solution of **27** (21.2 g, 118 mmol) in dichloromethane (70 mL) was added slowly through a syringe. The reaction mixture stirred at −78 °C for 1 h then triethylamine (67.8 mL, 487 mmol) was added slowly through a syringe. After a further 20 min at −78 °C, the reaction mixture warmed to rt and stirred for 1 h. The mixture was then poured onto saturated NaCl solution (300 mL), the aqueous layer separated, and extracted with diethyl ether (4 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude aldehyde.

(*tert*-Butoxycarbonylmethylene)triphenylphosphorane (44.4 g, 118 mmol) was added in several portions to a stirred solution of the crude aldehyde in dichloromethane (300 mL) at 0 °C. The reaction mixture was stirred for 14 h at rt, concentrated in vacuo and passed through a short pad of silica eluting with petroleum ether/diethyl ether (4:1) to afford enoate **28** (31.3 g, 96 %) an oil, as an inseparable mixture of geometric isomers [*E*/*Z*, >15:1; assigned by integration of the peaks at δ_H (major) = 6.87 (dt, $J = 15.6$, 6.9 Hz, 1H; CH$_2$C*H*=CH) and $\delta_H = 6.15$ (minor) (m, 1H; CH$_2$C*H*=CH)] which was used in the subsequent step without further purification. $R_f =$ 0.52 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (200 MHz; $CDCl_3$): $\delta =$ 7.35–7.31 (m, 5H; Ph), 6.87 (dt, $J = 15.6$, 7.0 Hz, 1H; CH$_2$C*H*=CH), 5.75 (dt, $J = 15.6$, 1.4 Hz, 1H; CH$_2$CH=C*H*), 4.50 (s, 2H; PhCH_2), 3.49 (t, $J =$ 6.3 Hz, 2H; PhCH$_2$OCH_2), 2.28 (qd, $J = 7.0$, 1.4 Hz, 2H; CH_2CH=CH), 1.76 (m, 2H; CH_2CH$_2$CH), 1.49 (s, 9H; C(CH_3)$_3$); ^{13}C NMR (50 MHz; $CDCl_3$): $\delta = 165.9$ (*CO*$_2$), 147.2 (CH$_2$*C*H=CH), 138.4 (*ipso C*-C), 128.3 (Ph), 127.5 (Ph), 127.5 (Ph), 123.3 (CH$_2$CH=*C*H), 79.9 (*C*(CH$_3$)$_3$), 72.9 (PhCH_2), 65.8 (PhCH$_2$OCH_2), 28.7 (CH_2), 28.2 (CH_2), 28.1 (C(CH_3)$_3$); IR (film): $\nu_{max} =$ 1713 (C=O), 1653 (C=C), 1496 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{17}H_{24}O_3$: C 73.9, H 8.75; found: C 74.1, H 8.86.

(5*S*)-3-[(*E*)-4-Benzyloxy-but-1-enyl]-2,5-dihydro-5-methyl-furan-2-one (8): *n*-Butyllithium (1.6 M in hexanes, 5.41 mL, 8.67 mmol) was added dropwise through a syringe to a solution of diisopropylamine (1.33 mL, 9.46 mmol) in THF (8.7 mL) at −78 °C. After 5 min at −78 °C, the solution was warmed to 0 °C over 10 min, then re-cooled to −78 °C. HMPA (1.57 mL, 9 mmol) was added in one portion through a syringe and the solution stirred at −78 °C for 30 min. A solution of **28** (2.18 g, 7.88 mmol) in THF (3 mL) was then added dropwise through a cannula to the lithium amide solution. Stirring was maintained at −78 °C for 1 h, then (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal (1.63 g, 8.67 mmol) in THF (2 mL) was added dropwise through a cannula. After a further 10 min at −78 °C, phosphate buffer solution (pH 7.2, 10 mL) was added and the reaction mixture warmed to rt. Following dilution with diethyl ether (200 mL), the organic phase was separated and washed with water (2 × 100 mL) and saturated NaCl solution (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude aldol product. This crude material was dissolved in a saturated solution of HCl in methanol (100 mL), stirred at rt for 5 min, then concentrated in vacuo. This process was repeated twice to afford the crude cyclised product. Methanesulfonyl chloride (0.91 mL, 11.8 mmol) was added dropwise through a syringe to a solution of this crude material and triethylamine (3.30 mL, 23.64 mmol) in dichloromethane (30 mL) at 0 °C. After 30 min at rt, the reaction mixture was diluted with dichloromethane (200 mL) and washed with HCl solution (1 M, 2 × 50 mL), saturated sodium hydrogen carbonate solution (50 mL) and saturated NaCl solution (50 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude diene **29**. Iodine (50 mg, 0.20 mmol) was added to a solution of **29** in chloroform (100 mL) at rt. The red solution was stirred for 4 h under irradiation (250 W sunlamp bulb), then concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (6:1 → 2:1) afforded diene **8** (1.15 g, 56 %), an oil, as an inseparable mixture of geometric isomers at the external olefin [*E*/*Z*, >95:5; assigned by integration of the peaks at δ_H (major) = 5.02 (br q, $J =$ 6.8 Hz, 1H; C*H*CH$_3$) and δ_H (minor) = 5.06 (m, 1H; C*H*CH$_3$)]. $R_f = 0.57$ (petroleum ether/diethyl ether 1:1); $[\alpha]_{29}^{D} = +27.4$ ($c = 0.31$ in CH_2Cl_2); ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 7.35-7.31$ (m, 5H; Ph), 7.05 (d, $J = 1.7$ Hz, 1H; C*H*CHO), 6.80 (dt, $J = 15.9$, 7.0 Hz, 1H; CH$_2$C*H*=CH), 6.20 (br d, $J =$ 15.9 Hz, 1H; CH$_2$CH=C*H*), 5.02 (br q, $J = 6.8$ Hz, 1H; C*H*CH$_3$), 4.53 (s, 2H; PhCH_2), 3.57 (t, $J = 6.7$ Hz, 2H; PhCH$_2$OCH_2), 2.50 (br q, $J = 6.8$ Hz, 2H; CH_2C=C), 1.42 (d, $J = 6.8$ Hz, 3H; CHCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): $\delta = 171.8$ (*CO*$_2$), 147.5 (*C*HCHO), 138.3 (*ipso C*-C), 134.8 (CH$_2$*C*H=CH), 129.2 (CH$_2$CH=*C*H), 128.4 (Ph), 127.7 (Ph), 127.6 (Ph), 120.2 (*C*CO$_2$), 76.9 (*C*HCH$_3$), 73.0 (PhCH_2), 69.1 (PhCH$_2$OCH_2), 33.8 (CH_2C=C), 19.1 (CHCH_3); IR (film): $\nu_{max} = 1753$ (C=O), 1662 (C=C), 1496 cm^{-1} (Ph); FAB-MS: *m*/*z*: calcd for $C_{16}H_{18}O_3$: 259.1334; found: 259.1334.

(3*S*,6*R*,9*R*)-6-(2′-Benzyloxy)-ethyl-3-methyl-4-phenyl-1,3,4,5,6,9-hexahydro-4-aza-5-oxo-isobenzofuran-1-one (32): Nitrosobenzene (2.92 g, 27.3 mmol) was added in one portion to a stirred solution of **8** (3.52 g, 13.6 mmol) in methanol/dichloromethane (1:1, 30 mL) at 0 °C. The solution turned aqua blue and was stirred at 0 °C for 21 h. Concentration in vacuo and purification by flash column chromatography eluting with petroleum ether/diethyl ether (4:1 → 2:1) afforded a yellow oil (4.57 g, 91 %), as a mixture of regioisomers (7:3, **30**/**31**) and diastereoisomers [>95:5 d.r. for the major regioisomer **30**, tentatively assigned by integration of the peaks at δ_H (major) = 6.96 (t, $J = 2.7$ Hz, 1H; CH=C) and δ_H (minor) = 7.07 (br s, 1H; C*H*=C)]. Further purification of the mixture of regio- and diastereoisomers by HPLC (hexane/THF 98:2; flow rate 40 mL min^{-1}) afforded HDA adduct **32** (2.75 g, 55 %, >98:2 d.r.). Retention time 30 min; $R_f = 0.30$ (petroleum ether/diethyl ether 1:1); $[\alpha]_{29}^{D} = -69$ ($c = 0.46$ in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): $\delta = 7.40$ (t, $J = 7.8$ Hz, 2H; NPhC*H*-*meta*), 7.30 (m, 8H; Ph), 6.96 (t, $J = 2.7$ Hz, 1H; C*H*=C), 4.82–4.78 (m, 1H; C*H*N), 4.48 (d, $J = 12.1$ Hz, 1H; PhC*H*H), 4.46 (d, $J = 12.1$ Hz, 1H; PhCH*H*), 4.32–4.28 (m, 1H; C*H*CH$_3$), 3.97 (dt, $J = 7.7$, 2.7 Hz, 1H; C*H*ON), 3.60–3.56 (m, 1H; OC*H*HCH$_2$), 3.56–3.50 (m, 1H; OCH*H*CH$_2$), 2.28–2.22 (m, 1H; OCH$_2$C*H*H), 2.05–1.96 (m, 1H; OCH$_2$CH*H*), 0.98 (d, $J = 6.3$ Hz, 3H; CHCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): $\delta = 167.3$ (*CO*$_2$), 148.4 (*ipso C*-N), 138.2 (*ipso C*-C), 137.6 (*C*H=CCO$_2$), 129.2 (NPh*C*H-*meta*), 129.1 (Ph), 128.3 (Ph), 127.9 (2 × Ph), 127.5 (Ph), 123.7 (CH=*C*CO$_2$), 78.0 (*C*HON), 74.3 (PhCH_2), 73.0 (*C*HOCH$_3$), 69.8 (*C*HN), 66.3 (O*C*H$_2$CH$_2$), 33.5 (OCH$_2$*C*H$_2$), 19.3 (CH*C*H$_3$); IR (film): $\nu_{max} = 1771$ (C=O), 1595 (C=C), 1490 cm^{-1} (Ph); ES-MS: *m*/*z*: calcd for $C_{22}H_{23}NO_4Na$: 388.1543; found: 388.1525.

(2′*R*,4*R*,5*S*)-3-(4′-Benzyloxy-2′-hydroxy-butylidene)-4-*N*-phenylamino-dihydro-5-methyl-furan-2-one (33): A solution of [Mo(CO)$_6$] (1.45 g, 5.48 mmol) in anhydrous acetonitrile (14 mL) was heated at reflux under argon for 4 h, then allowed to cool to rt. A solution of **32** (1.00 g, 2.74 mmol) in acetonitrile (3 mL) was added dropwise through a syringe and the reaction mixture stirred at rt for 15 min, then water (2 mL) was added. After stirring for a further 45 min at rt, the reaction mixture was concentrated in vacuo and passed through a short pad of silica eluting with petroleum ether/diethyl ether (1:2) to afford a pale purple oil. This was further purified by flash column chromatography eluting with dichloromethane/diethyl ether (95:5) to afford amino alcohol **33** (650 mg, 70 %) as an oil that solidified on standing. The solid could be recrystallised from dichloromethane/ether/pentane to give fine white needles. M.p. 82 °C; $R_f =$ 0.41 (diethyl ether); $[\alpha]_{29}^{D} = +79$ ($c = 0.50$ in CH_2Cl_2); ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 7.34-7.25$ (m, 5H; Ph), 7.21 (br t, $J = 7.7$ Hz, 2H; NPhC*H*-*meta*), 6.99 (dd, $J = 6.3$, 1.6 Hz, 1H; C*H*=CCO$_2$), 6.84 (br t, $J = 7.7$ Hz, 1H; NPhC*H*-*para*), 6.61 (br d, $J = 7.7$ Hz, 2H; NPhC*H*-*ortho*), 4.76 (q, $J =$ 6.3 Hz, 1H; C*H*CH=C), 4.60–4.54 (br m, 1H; C*H*N), 4.54–4.48 (m, 1H; C*H*CH$_3$), 4.48 (q (AB), $J = 11.9$ Hz, 2H; PhCH_2), 4.40–3.80 (br m, 2H; O*H*, N*H*), 3.70–3.55 (m, 2H; OCH_2CH$_2$), 1.97–1.87 (m, 2H; OCH$_2$CH_2), 1.38 (d, $J = 6.4$ Hz, 3H; CHCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): $\delta = 169.9$ (*CO*$_2$), 147.6 (*ipso C*-N), 145.5 (*C*H=CCO$_2$), 137.7 (*ipso C*-C), 129.6 (Ph), 128.5 (Ph), 127.8 (Ph), 127.8 (Ph), 127.6 (Ph), 119.7 (CH=*C*CO$_2$), 114.7 (NPh*C*-*ortho*), 80.5 (O*C*HC=C), 73.2 (PhCH_2), 68.5 (*C*HCH$_3$), 67.2, (O*C*H$_2$CH$_2$), 57.2 (*C*HN), 36.2 (OCH$_2$*C*H$_2$), 21.0 (CH*C*H$_3$); IR (KBr):

ν_{max} = 3375 (br, O-H and N-H), 1752 (C=O), 1680 (C=C), 1601, 1497 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{22}H_{25}NO_4$: C 71.9, H 6.86, N 3.8; found: C 71.8, H 6.87, N 3.8.

(2′*R*,4*R*,5*S*)-3-(4′-Benzyloxy-2′-(*tert*-butyldimethylsilyloxy)-butylidene)-4-*N*-phenylamino-dihydro-5-methyl-furan-2-one (34): *tert*-Butyldimethylchlorosilane (590 mg, 3.92 mmol) was added in one portion to a solution of **33** (480 mg, 1.30 mmol) and imidazole (440 mg, 6.53 mmol) in DMF (2.5 mL) at rt. After stirring for 14 h at rt, the reaction mixture was diluted with diethyl ether (75 mL), washed with water (30 mL) and saturated NaCl solution (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (9:1 → 2:1) afforded silyl ether **34** (520 mg, 83 %) as an oil. R_f = 0.70 (petroleum ether/diethyl ether 1:1); $[\alpha]_{29}^{D}$ = +86 (c = 0.49 in CH_2Cl_2); ^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.33 – 7.24 (m, 5H; Ph), 7.16 (br t, J = 7.5 Hz, 2.0H; NPhC*H-meta*), 6.98 (dd, J = 7.1, 1.9 Hz, 1H; C*H*=CCO$_2$), 6.77 (br t, J = 7.5 Hz, 1H; NPhC*H-para*), 6.45 (br d, J = 7.5 Hz, 2H; NPhC*H-ortho*), 4.84 (q, J = 7.1 Hz, 1H; C*H*CH=C), 4.55 (qd, J = 6.5, 2.0 Hz, 1H; C*H*CH$_3$), 4.50 (s, 2H; PhCH_2), 4.47 (m, 1H; C*H*N), 3.91 (d, J = 5.6 Hz, 1H; N*H*), 3.58 (t, J = 6.1 Hz, 2H; OCH_2CH$_2$), 2.06 – 1.97 (m, 1H; OCH$_2$C*H*H), 1.97 – 1.90 (m, 1H; OCH$_2$CH*H*), 1.38 (d, J = 6.5 Hz, 3H; CHCH_3), 0.85 (s, 9H; C(CH_3)$_3$), −0.03 (s, 3H; SiCH_3), −0.05 (s, 3H; SiCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 169.7 (*C*O$_2$), 149.1 (*ipso C*-N), 145.4 (*C*H=CCO$_2$), 138.0 (*ipso C*-C), 129.5 (Ph), 128.4 (Ph), 127.6 (Ph), 127.5 (Ph), 126.2 (Ph), 118.7 (CH=*C*CO$_2$), 113.5 (NPh*C-ortho*), 79.9 (*C*HCH=C), 72.9 (PhCH$_2$), 66.9 (*C*HCH$_3$), 65.9, (O*C*H$_2$CH$_2$), 56.1 (*C*HN), 37.5 (OCH$_2$*C*H$_2$), 25.7 (C(*C*H$_3$)$_3$), 20.7 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.5 (Si*C*H$_3$), −5.1 (Si*C*H$_3$); IR (film): ν_{max} = 3354 (br, N-H), 1754 (C=O), 1680 (C=C), 1601, 1489 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{28}H_{39}NO_4Si$: C 69.8, H 8.16, N 2.9; found: C 69.8, H 8.14, N 3.0.

(2′*S*,3*R*,4*R*,5*S*)-3-(4′-Benzyloxy-2′-*tert*-butyldimethylsilyloxy)-butyl-4-*N*-phenylamino-2,3,4,5-tetrahydro-5-methyl-furan-2-one (35): Methanol (3 mL) was added to a mixture of **34** (85 mg, 0.176 mmol) and PtO_2 (30 mg, 33 mol %), and the reaction was placed under an hydrogen atmosphere. After stirring at rt for 90 min, the catalyst was removed by filtration through a small pad of silica eluting with diethyl ether. Concentration in vacuo afforded amine **35** (83 mg, 98 %) an oil, as a single diastereoisomer, which required no further purification. R_f = 0.24 (petroleum ether/diethyl ether 1:1); $[\alpha]_{29}^{D}$ = −30.5 (c = 0.49 in CH_2Cl_2); ^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.37 – 7.27 (m, 5H; Ph), 7.16 (dd, J = 8.6, 7.4 Hz, 2H; NPhC*H-meta*), 6.74 (br t, J = 7.4 Hz, 1H; NPhC*H-para*), 6.56 (br d, J = 8.6 Hz, 2H; NPhC*H-ortho*), 4.46 (s, 2H; PhCH_2), 4.20 – 4.14 (m, 2H; C*H*OSi, C*H*CH$_3$), 3.77 – 3.47 (m, 4H; C*H*N, N*H*, OCH_2CH$_2$), 2.66 (dt, J = 9.2, 6.5 Hz, 1H; C*H*CO$_2$), 2.11 – 1.97 (m, 1H; CH(O)C*H*H), 1.86 – 1.73 (m, 3H; OCH$_2$CH_2, CH(O)CH*H*), 1.46 (d, J = 6.3 Hz, 3H; CHCH_3), 0.88 (s, 9H; C(CH_3)$_3$), 0.03 (s, 6H; 2 × SiCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 176.3 (*C*O$_2$), 146.3 (*ipso C*-N), 138.4 (*ipso C*-C), 129.4 (Ph), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 118.5 (Ph), 113.2 (Ph), 80.8 (*C*HCH$_3$), 73.0 (PhCH$_2$), 67.2 (*C*HOSi), 66.5 (O*C*H$_2$CH$_2$), 62.6 (*C*HN), 44.1 (*C*HCO$_2$), 36.6 (OCH$_2$*C*H$_2$), 36.5 (CH(O)*C*H$_2$), 25.9 (C(*C*H$_3$)$_3$), 19.4 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.4 (Si*C*H$_3$), −4.6 (Si*C*H$_3$); IR (film): ν_{max} = 3373 (br, N-H), 1770 (C=O), 1601, 1497 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{28}H_{41}NO_4Si$: C 69.5, H 8.54, N 2.9; found: C 69.0, H 8.76, N 3.0.

(2′*S*,3*R*,4*R*,5*S*)-3-(4′-Benzyloxy-2′-*tert*-butyldimethylsilyloxy)-butyl-4-*N*-phenyl-*N*-trifluoroacetamido-2,3,4,5-tetrahydro-5-methyl-furan-2-one (36): Trifluoroacetic anhydride (74 μL, 0.516 mmol) was added dropwise through a syringe to a solution of **35** (83 mg, 0.172 mmol) and Hünig's base (123 μL, 0.704 mmol) in dichloromethane (4 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was diluted with diethyl ether (50 mL), washed with water (30 mL) and saturated NaCl solution (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (1:1) afforded trifluoroacetamide **36** (92 mg, 95 %) as an oil. R_f = 0.43 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.51 – 7.43 (m, 3H; N-Ph), 7.35 – 7.26 (m, 5H; Ph), 7.13 (br d, J = 5.9 Hz, 2H; NPhC*H-ortho*), 4.85 (dd, J = 9.0, 7.7 Hz, 1H; C*H*N), 4.50 (d, J = 11.9 Hz, 1H; PhC*H*H), 4.45 (d, J = 11.9 Hz, 1H; PhC*H*H), 4.39 (qn, J = 6.7 Hz, 1H; CHOSi), 4.37 – 4.31, (m, 1H; C*H*CH$_3$), 3.61 – 3.52 (m, 2H; OCH_2CH$_2$), 2.73 – 2.67 (m, 1H; C*H*CO$_2$), 2.02 – 1.94 (m, 1H; C*H*HCHCO$_2$), 1.94 – 1.87 (m, 2H; OCH$_2$CH_2), 1.81 – 1.68 (m, 1H; CH(O)CH*H*), 1.53 (d, J = 6.3 Hz, 3H; CHCH_3), 0.88 (s, 9H; C(CH_3)$_3$), 0.08 (s, 3H; SiCH_3), 0.07 (s, 3H; SiCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): δ = 175.0 (*C*O$_2$), 138.4 (*ipso C*-N), 134.5 (*ipso C*-C), 130.4 (Ph), 130.2 (Ph), 130.0 (Ph), 129.9 (Ph), 128.4 (Ph), 127.7 (Ph), 127.6 (Ph), 76.2 (*C*HCH$_3$), 73.1 (PhC*H*$_2$), 67.1 (*C*HOSi), 66.7 (O*C*H$_2$CH$_2$), 65.5 (*C*HN), 39.4 (*C*HCO$_2$), 37.1 (OCH$_2$*C*H$_2$), 36.2 (CH(O)*C*H$_2$), 25.9 (C(*C*H$_3$)$_3$), 19.3 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.2 (Si*C*H$_3$), −4.6 (Si*C*H$_3$); IR (film): ν_{max} = 2930, 2857 (C-H), 1782 (OC=O), 1699 (PhNC=O), 1596, 1537, 1493 cm^{-1} (Ph); ES-MS: m/z: calcdc for $C_{30}H_{40}F_3NO_5SiNa$: 602.2526; found:602.2523.

(2′*S*,3*R*,4*R*,5*S*)-3-(4′-Hydroxy-2′-*tert*-butyldimethylsilyloxy)-butyl-4-*N*-phenyl-*N*-trifluoroacetamido-2,3,4,5-tetrahydro-5-methyl-furan-2-one (37): Methanol (3 mL) was added to a mixture of **36** (92 mg, 0.163 mmol) and palladium hydroxide (40 mg, 40 %), and the reaction mixture was placed under a hydrogen atmosphere. After stirring at rt for 48 h, the catalyst was removed by filtration through a small pad of silica eluting with diethyl ether and all volatiles were removed in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (1:2) afforded alcohol **37** (76 mg, 95 %) as an oil. R_f = 0.16 (petroleum ether/diethyl ether 1:2); $[\alpha]_{29}^{D}$ = +30.6 (c = 1.87 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.54 – 7.50 (m, 3H; N-Ph), 7.29 (br d, J = 6.4 Hz, 1H; N-Ph), 7.16 (br d, J = 6.4 Hz, 1H; N-Ph), 4.85 (dd, J = 9.7, 8.3 Hz, 1H; C*H*N), 4.47 – 4.43 (m, 1H; C*H*OSi), 4.43 – 4.38 (m, 1H; C*H*CH$_3$), 3.77 (br s, 2H; CH_2OH), 2.73 – 2.69 (m, 1H; C*H*CO$_2$), 2.10 (br s, 1H; O*H*), 2.02 – 1.94 (m, 2H; CH_2CHCO$_2$), 1.80 – 1.75 (m, 1H; CH$_2$C*H*H), 1.68 – 1.63 (m, 1H; CH$_2$C*H*H), 1.55 (d, J = 6.3 Hz, 3H; CHCH_3), 0.91 (s, 9H; C(CH_3)$_3$), 0.13 (s, 3H; SiCH_3), 0.12 (s, 3H; SiCH_3); ^{13}C NMR (150 MHz; $CDCl_3$): δ = 174.6 (*C*O$_2$), 158.1 (q, J = 36, F$_3$C*C*O$_2$), 138.8 (*ipso C*-N), 130.5 (Ph), 130.0 (Ph), 130.0 (Ph), 129.8 (Ph), 129.7 (Ph), 75.6 (*C*HCH$_3$), 71.1 (*C*HOSi), 68.2 (*C*HN), 65.7 (*C*H$_2$OH), 39.7 (*C*HCO$_2$), 37.5 (OCH$_2$*C*H$_2$), 36.2 (*C*H$_2$CHCO$_2$), 25.8 (C(*C*H$_3$)$_3$), 19.0 (CH*C*H$_3$), 17.9 (*C*(CH$_3$)$_3$), −4.3 (Si*C*H$_3$), −4.7 (Si*C*H$_3$); IR (film): ν_{max} = 3480 (br, O-H), 2931, 2858 (C-H), 1779 (OC=O), 1698 (PhNC=O), 1596, 1493 cm^{-1} (Ph); elemental analysis calcd (%) for $C_{23}H_{34}F_3NO_5Si$: C 56.4, H 6.99, N 2.9; found: C 56.6, H 6.86, N 3.0; ES-MS: m/z: calcd for $C_{23}H_{34}F_3NO_5SiNa$: 512.2056; found: 512.2027.

(*Z*/*E*)-(2′*S*,3*R*,4*R*,5*S*)-3-(5′-Iodo-2′-*tert*-butyldimethylsilyloxy)-pent-4′-enyl-4-*N*-phenyl-*N*-trifluoroacetamido-2,3,4,5-tetrahydro-5-methyl-furan-2-one (38)

1) Oxidation of 37 to the aldehyde: A solution of dimethyl sulfoxide (36 μL, 0.512 mmol) in dichloromethane (1 mL) was added dropwise through a syringe to a vigorously stirred solution of oxalyl chloride (41 μL, 0.465 mmol) in dichloromethane (2 mL) at −78 °C. After 30 min at −78 °C, a solution of **37** (75 mg, 0.155 mmol) in dichloromethane (2 mL) was added dropwise through a syringe. The temperature was maintained at −78 °C for a further 30 min, then triethylamine (0.2 mL, 1.40 mmol) was added dropwise through a syringe. After warming to rt over 45 min, the reaction mixture was diluted with diethyl ether (100 mL), washed with phosphate buffer solution (pH 7.2, 20 mL) and saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The oil was passed through a small pad of silica eluting with diethyl ether, to afford after removal of volatiles, the aldehyde (73 mg, 96 %) which was used in the subsequent step without further purification. R_f = 0.34 (petroleum ether/diethyl ether 1:2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.79 (d, J = 3.0 Hz, 1H; C*H*O), 7.55 – 7.49 (m, 3H; Ph), 7.34 – 7.28 (br s, 1H; Ph), 7.15 (br d, J = 6.2 Hz, 1H; Ph), 4.89 (dd, J = 9.9, 8.3 Hz, 1H; C*H*N), 4.79 – 4.74 (m, 1H; C*H*OSi), 4.38 (dq, J = 8.3, 6.3 Hz, 1H; C*H*CH$_3$), 2.74 (dd, J = 9.9, 4.2 Hz, 1H; C*H*CO$_2$), 2.68 (dd, J = 15.6, 4.3 Hz, 1H; C*H*HCHO), 2.46 (ddd, J = 15.6, 5.7, 3.0 Hz, 1H; CH*H*CHO), 2.06 (ddd, J = 14.2, 9.4, 4.7 Hz, 1H; CH*H*CHCO$_2$), 1.93 (ddd, J = 14.2, 7.8, 4.2 Hz, 1H; CH*H*CHCO$_2$), 1.55 (d, J = 6.3 Hz, 3H; CHCH_3), 0.89 (s, 9H; C(CH_3)$_3$), 0.11 (s, 3H; SiCH_3), 0.11 (s, 3H; SiCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 201.5 (*C*HO), 174.5 (*C*O$_2$), 158.0 (q, J = 36, F$_3$C*C*O$_2$), 134.3 (*ipso C*-N), 130.6 (Ph), 130.2 (Ph), 129.8 (Ph), 75.4 (*C*HCH$_3$), 65.4 (*C*HOSi), 65.3 (*C*HN), 49.5 (*C*H$_2$CHO), 39.2 (*C*HCO$_2$), 36.5 (*C*H$_2$CHCO$_2$), 25.8 (C(*C*H$_3$)$_3$), 18.8 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.4 (Si*C*H$_3$), −4.8 (Si*C*H$_3$).

2) Homologation to the vinyl iodide: A solution of the above aldehyde (73 mg, 0.150 mmol) and iodoform (181 mg, 0.465 mmol) in THF (3 mL) was added via cannular to a rapidly stirred slurry of chromium dichloride (191 mg, 1.55 mmol) in THF at 0 °C. A deep red colouration was observed after complete addition. After stirring for 14 h, the reaction mixture was diluted with diethyl ether (60 mL), washed with water (2 × 30 mL) and saturated NaCl solution (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with

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petroleum ether/diethyl ether (2:1) afforded vinyl iodide **38** (68 mg, 75%), an oil, as an inseparable mixture of geometric isomers [*E*/*Z* 4:1; assigned by integration of the ^{1}H NMR peaks at δ_H (major) = 6.09 (d, J = 14.5 Hz, 1H; C*H*I) and δ_H (minor) = 6.38–6.32 (m, 2H; C*H*I, C*H*=CHI)]. R_f = 0.42 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 7.53–7.50 (m, 3H; Ph), 7.23 (brs, 1H; Ph), 7.16 (brs, 1H; Ph), 6.55 (dt, J = 14.5, 7.5 Hz, 1H; C*H*=CHI), 6.09 (d, J = 14.5 Hz, 1H; C*H*I), 4.79 (dd, J = 9.4, 8.0 Hz, 1H; C*H*N), 4.48–4.41 (m, 1H; C*H*OSi), 4.31–4.27 (m, 1H; C*H*CH_3), 2.77–2.72 (m, 1H; C*H*CO_2), 2.29–2.23 (m, 1H; C*H*HCHCO$_2$), 2.20–2.13 (m, 1H; CH*H*CHCO$_2$), 1.95–1.83 (m, 2H; CH_2CH=C), 1.54 (d, J = 6.3 Hz, 3H; CHCH_3), 0.90 (s, 9H; C(CH_3)$_3$), 0.09 (s, 3H; SiCH_3), 0.08 (s, 3H; SiCH_3); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor) = 7.53–7.50 (m, 3H; Ph), 7.23 (brs, 1H; Ph), 7.16 (brs, 1H; Ph), 6.38–6.32 (m, 2H; C*H*I, C*H*=CHI), 4.91–4.87 (m, 1H; C*H*N), 4.41–4.36 (m, 1H; C*H*OSi), 4.31–4.27 (m, 1H; C*H*CH_3), 2.77–2.72 (m, 1H; C*H*CO_2), 2.33 (t, J = 5.7 Hz, 1H; C*H*HCHCO$_2$), 2.29–2.23 (m, 1H; CH*H*CHCO$_2$), 1.95–1.83 (m, 2H; CH_2CH=C), 1.55 (d, J = 6.3 Hz, 3H; CHCH_3), 0.90 (s, 9H; C(CH_3)$_3$), 0.10 (s, 3H; SiCH_3), 0.09 (s, 3H; SiCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 174.4 (*C*O_2), 158.0 (q, J = 36, F_3CCO_2), 142.3 (*C*H=CHI), 134.9 (*ipso C*-N), 130.5 (Ph), 130.1 (Ph), 129.8 (Ph), 77.4 (CH=*C*HI), 75.7 (*C*HCH$_3$), 67.9 (*C*HOSi), 66.2 (*C*HN), 42.5 (*C*H_2CH=C), 39.3 (*C*HCO_2), 36.3 (*C*H_2CHCO$_2$), 25.9 (C(*C*H$_3$)$_3$), 19.1 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.4 (Si*C*H$_3$), −4.5 (Si*C*H$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ (minor) = 174.6 (*C*O_2), 158.0 (q, J = 36, F_3CCO_2), 137.2 (*C*H=CHI), 134.9 (*ipso C*-N), 130.5 (Ph), 130.1 (Ph), 129.7 (Ph), 84.7 (CH=*C*HI), 75.8 (*C*HCH$_3$), 67.9 (*C*HOSi), 65.6 (*C*HN), 41.6 (*C*H_2CH=C), 39.6 (*C*HCO_2), 36.6 (*C*H_2CHCO$_2$), 25.9 (C(*C*H$_3$)$_3$), 19.1 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.4 (Si*C*H$_3$), −4.5 (Si*C*H$_3$); IR (film): ν_{max} = 2929, 2856 (C-H), 1780 (OC=O), 1698 (PhNC=O), 1596, 1492 cm^{-1} (Ph); ES-MS: *m*/*z*: calcd for $C_{24}H_{33}F_3INO_4SiNa$: 634.1073; found: 634.1069.

(*Z*/*E*)-(2′*R*,5*S*)-3-(5′-Iodo-2′-*tert*-butyldimethylsilyloxy)-pent-4′-enyl-2,5-dihydro-5-methyl-furan-2-one (5): 1,8-Diazabicyclo[5.4.0]undec-7-ene (36 μL, 0.24 mmol) was added dropwise through a syringe to a solution of **38** (67 mg, 0.11 mmol) in dichloromethane (2 mL) at 0 °C. After stirring at 0 °C for 1 h, saturated ammonium chloride (1 mL) was added, and then the reaction mixture was poured onto diethyl ether (50 mL). The organic phase was separated, washed with water (20 mL) and saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with dichloromethane afforded butenolide **5** (42 mg, 91%) an oil, as in separable mixture of geometric isomers [*E*/*Z* 4:1; tentatively assigned by integration of the ^{1}H NMR peaks at δ_H (major) = 6.07 (d, J = 14.4 Hz, 1H; C*H*I) and δ_H (minor) = 6.34–6.30 (m, 2H; C*H*I, C*H*=CHI)]. R_f = 0.45 (dichloromethane); ^{1}H NMR (600 MHz; $CDCl_3$): δ (major) = 7.11 (brs, 1H; C=C*H*), 6.53 (dt, J = 14.4, 7.4 Hz, 1H; C*H*C=CHI), 6.07 (d, J = 14.4 Hz, 1H; C*H*I), 5.02 (brq, J = 7.0 Hz, 1H; C*H*CH$_3$), 4.06 (qn, J = 5.7 Hz, 1H; C*H*OSi), 2.46–2.40 (m, 2H; CH_2CCO$_2$), 2.26–2.17 (m, 2H; CH$_2$CH=C), 1.42 (d, J = 7.0 Hz, 3H; CHCH_3), 0.88 (s, 9H; C(CH_3)$_3$), 0.06 (s, 3H; SiCH_3), 0.03 (s, 3H; SiCH_3); ^{1}H NMR (600 MHz; $CDCl_3$): δ (minor) = 7.15 (brs, 1H; C=C*H*), 6.34–6.30 (m, 2H; C*H*I, C*H*=CHI), 4.99 (brq, J = 6.9 Hz, 1H; C*H*CH$_3$), 4.16 (qn, J = 5.7 Hz, 1H; C*H*OSi), 2.46–2.40 (m, 1H; C*H*HCCO$_2$), 2.36–2.31 (m, 1H; CH*H*CCO$_2$), 2.26–2.17 (m, 2H; CH_2CH=C), 1.43 (d, J = 6.9 Hz, 3H; CHCH_3), 0.87 (s, 9H; C(CH_3)$_3$), 0.09 (s, 3H; SiCH_3), 0.05 (s, 3H; SiCH_3); ^{13}C NMR (150 MHz; $CDCl_3$): δ (major) = 173.7 (*C*O_2), 151.9 (C=*C*H), 142.3 (*C*H=CHI), 130.4 (*C*=CH), 77.5 (*C*HCH$_3$), 77.2 (CH=*C*HI), 68.6 (*C*HOSi), 43.4 (*C*H_2CH=C), 33.0 (*C*H_2CCO$_2$), 25.8 (C(*C*H$_3$)$_3$), 18.9 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.5 (Si*C*H$_3$), −4.6 (Si*C*H$_3$); ^{13}C NMR (150 MHz; $CDCl_3$): δ (minor) = 173.7 (*C*O_2), 152.1 (C=*C*H), 137.2 (*C*H=CHI), 130.4 (*C*=CH), 84.7 (CH=*C*HI), 77.7 (*C*HCH$_3$), 68.4 (*C*HOSi), 43.6 (*C*H_2CH=C), 32.8 (*C*H_2CCO$_2$), 25.8 (C(*C*H$_3$)$_3$), 19.1 (CH*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.6 (Si*C*H$_3$), −4.8 (Si*C*H$_3$); IR (film): ν_{max} = 2928, 2855 (C-H), 1754 (C=O), 1604 cm^{-1} (C=C); ES-MS: *m*/*z*: calcd for $C_{16}H_{27}O_3ISiNa$: 445.0672; found: 445.0680.

The final steps: Detailing the synthesis of muricatetrocin C from fragments **3**, **4** and **5**. In this section the compounds are discussed in terms of the numbering system used for this family of natural products. Thus, the butenolide carbonyl carbon is C-1, and the terminal methyl group of the aliphatic chain is C-32.

(12*R*,15*S*,16*R*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxyprop-17-ynyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (40) and **(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxyprop-17-ynyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (41)**: *n*-Butyllithium (1.6 M in hexanes, 2.35 mL, 3.76 mmol) was added dropwise through a syringe to a solution of **15** (970 mg, 1.88 mmol) in THF (2.4 mL) at −78 °C. After 30 min at −78 °C, a solution of **4** (350 mg, 1.40 mmol) in THF (2.5 mL) was added dropwise via cannular. The reaction was warmed to −20 °C over 30 min, then saturated ammonium chloride solution (2 mL) was added. Once at rt, the reaction mixture was diluted with diethyl ether (100 mL), washed with water (50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (10:1 → 1:2) afforded propargylic alcohols **40** and **41** (540 mg, 63%) an oil, as an inseparable mixture of C-16 epimers [**40**/**41** 1.8:1; assigned by integration of the peaks at δ_H (major) = 3.36 (s, 3H; $C_{34}OCH_3$) and δ_H (minor) = 3.35 (s, 3H; $C_{34}OCH_3$)]. R_f = 0.14 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (600 MHz; $CDCl_3$): δ (mixture) = 7.34–7.33 (m, 3H; Ph), 7.29–7.26 (m, 2H; Ph), 4.50 [brs, 3H; PhCH_2, *H*-16 (major)], 4.38–4.37 (m, 1H; *H*-19), 4.26 [d, J = 6.1 Hz, 1H; *H*-16 (minor)], 4.14 (dt, J = 7.5, 3.4 Hz, 1H; *H*-15), 4.09–4.06 (m, 1H; *H*-12), 3.99–3.94 (m, 1H; *H*-20), 3.51–3.47 (m, 2H; H_2-9), 3.36 [s, 3H; $C_{34}OCH_3$ (major)], 3.35 [s, 3H; $C_{34}OCH_3$ (minor)], 3.24 (s, 3H; $C_{35}OCH_3$), 2.40 (brs, 1H; O*H*), 2.09–2.05 (m, 1H; *H*-13), 2.02–1.99 (m, 2H; H_2-14), 1.74–1.69 (m, 1H; *H*-10), 1.68–1.61 (m, 4H, *H*-10; H_2-11, *H*-21), 1.58–1.52 (m, 1H; *H*-13), 1.48–1.45 (m, 1H; *H*-21), 1.31 (s, 3H; $C_{34}CH_3$), 1.30–1.23 (m, 20H; H_2-22 → H_2-31), 1.27 (s, 3H; $C_{35}CH_3$), 0.88 (t, J = 7.0 Hz, 3H; H_3-32); ^{13}C NMR (150 MHz; $CDCl_3$): δ (mixture) = 138.6 (*ipso C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 99.4 (*C*-34), 98.2 (*C*-35), 83.7 [*C*-17 (minor)], 83.5 [*C*-17 (major)], 82.8 [*C*-18 (major)], 82.6 [*C*-18 (minor)], 81.5 [*C*-12 (minor)], 80.8 [*C*-15 (major)], 80.6 [*C*-12 (major)], 79.7 [*C*-15 (minor)], 72.8 (Ph*C*H_2), 70.3 [*C*-9 (major)], 70.2 [*C*-9 (minor)], 67.7 (*C*-20), 65.4 [*C*-16 (minor)], 64.7 [*C*-16 (major)], 63.8 (*C*-19), 49.6 ($C_{34}OCH_3$), 47.9 ($C_{35}OCH_3$), 32.3 [*C*-13 (major)], 32.2 [*C*-13 (minor)], 32.0 [*C*-11 (minor)], 31.9 [*C*-11 (major)], 31.5 [*C*-21 (minor)], 30.3 [*C*-21 (major)], 29.7–29.6 (7 × *C*H_2), 29.3 (*C*H_2), 26.6 (*C*-14), 26.4 (*C*-10), 25.2 (*C*H_2), 22.7 (*C*H_2), 18.3 ($C_{35}CH_3$), 18.0 ($C_{34}CH_3$), 14.1 (*C*-32); IR (film): ν_{max} = 3443 (br, O-H), 2921, 2856 (C-H), 1588 cm^{-1} (Ph); ES-MS: *m*/*z*: calcd for $C_{37}H_{60}O_7Na$: 639.4237; found: 639.4267.

(12*R*,15*S*,16*R*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxypropyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (42) and **(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxypropyl)-tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (43)**: A slurry of Raney nickel (50% in water, 2.0 g), was washed successively with 95% ethanol (3 × 5 mL) and absolute ethanol (3 × 5 mL), then suspended in absolute ethanol (3 mL) and placed under an hydrogen atmosphere. A solution of **40** and **41** (490 mg, 0.790 mmol) in absolute ethanol (3 mL) was added dropwise through a syringe and the reaction stirred vigorously for 1 h at rt. Filtration through a short plug of silica eluting with diethyl ether and concentration in vacuo afforded alcohols **42** and **43** (440 mg, 89%), an oil, as a mixture of *C*-16 epimers (**42**/**43** 1.8:1; assigned by integration of the peaks at δ_H (major) = 3.31 (s, 3H; $C_{34}OCH_3$) and δ_H (minor) = 3.28 (s, 3H; $C_{34}OCH_3$) in the crude ^{1}H NMR). Further purification by flash column chromatography eluting with petroleum ether/diethyl ether (1:1) afforded **43** (90 mg, 18%) and a mixture of **42** and **43** (350 mg, 71%). R_f = 0.33 (major; petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D}$ (major) = −38 (c = 0.85 in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): δ(major) = 7.35–7.33 (m, 4H; Ph), 7.29–7.27 (m, 1H; Ph), 4.50 (s, 2H; PhCH_2), 4.08–4.06 (m, 1H; *H*-20), 3.99–3.97 (m, 1H; *H*-12), 3.91–3.88 (m, 1H; *H*-15), 3.80–3.78 (m, 1H; *H*-16), 3.52–3.48 (m, 3H; H_2-9, *H*-19), 3.31 (s, 3H; $C_{34}OCH_3$), 3.24 (s, 3H; $C_{35}OCH_3$), 2.17–2.14 (m, 1H; *H*-18), 2.02–2.07 (m, 2H; *H*-13, O*H*), 1.87–1.82 (m, 2H; H_2-14), 1.75–1.67 (m, 2H; *H*-10, *H*-17), 1.67–1.61 (m, 2H; *H*-10, *H*-11), 1.56–1.43 (m, 5H; *H*-11, *H*-13, *H*-17, *H*-18, *H*-21), 1.33–1.21 (m, 21H; *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.27 (s, 3H; $C_{35}CH_3$), 0.88 (t, J = 7.0 Hz, 3H; H_3-32); ^{13}C NMR (150 MHz; $CDCl_3$): δ (major) = 138.6 (*ipso C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 99.7 (*C*-34), 98.7 (*C*-35), 81.5 (*C*-15), 79.8 (*C*-12), 74.3 (*C*-19), 72.8 (Ph*C*H_2), 71.7 (*C*-16), 70.3 (*C*-9), 68.8 (*C*-20), 49.7 ($C_{35}OCH_3$), 47.8 ($C_{34}OCH_3$), 32.6 (*C*-11), 32.2 (*C*-13), 31.9 (*C*H_2), 31.4 (*C*-17), 30.0 (*C*H_2), 29.7–29.6 (6 × *C*H_2), 29.3 (*C*H_2), 26.4 (*C*H_2), 26.0 (*C*-10), 25.1 (*C*-14), 24.7 (*C*-18), 22.7 (*C*H_2), 18.8 ($C_{34}CH_3$), 18.2 ($C_{35}CH_3$), 14.1 (*C*-32); IR (film): ν_{max} (major) = 3445 (br, O-H), 2920, 2850 cm^{-1} (C-H). R_f = 0.29 (minor; petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D}$ (minor) = −42 (c = 0.95 in CH_2Cl_2); ^{1}H NMR (600 MHz; $CDCl_3$): δ

(minor) = 7.35 – 7.33 (m, 4H; Ph), 7.29 – 7.27 (m, 1H; Ph), 4.50 (s, 2H; PhCH_2), 4.07 – 4.04 (m, 1H; *H*-20), 3.91 (qn, J = 6.0 Hz, 1H; *H*-12), 3.80 (q, J = 7.0 Hz, 1H; *H*-15), 3.51 – 3.46 (m, 3H; H_2-9, *H*-19), 3.38 – 3.36 (m, 1H; *H*-16), 3.28 (s, 3H; $C_{34}OCH_3$), 3.24 (s, 3H; $C_{35}OCH_3$), 2.42 (d, J = 3.5 Hz, 1H; O*H*), 2.04 – 1.98 (m, 3H; *H*-13, *H*-14, *H*-18), 1.81 – 1.50 (m, 10H; H_2-10, H_2-11, *H*-13, *H*-14, H_2-17, *H*-18, *H*-21), 1.32 – 1.23 (m, 21H; *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.27 (s, 3H; $C_{35}CH_3$), 0.88 (t, J = 7.0 Hz, 3H; H_3-32); ^{13}C NMR (150 MHz; $CDCl_3$): δ(minor) = 138.6 (*ipso* *C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 99.7 (*C*-34), 98.9 (*C*-35), 82.0 (*C*-15), 79.0 (*C*-12), 75.2 (*C*-19), 74.9 (*C*-16), 72.9 (PhCH_2), 70.2 (*C*-9), 68.9 (*C*-20), 49.6 ($C_{35}OCH_3$), 47.7 ($C_{34}OCH_3$), 32.4 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.7 – 29.6 (6 × CH_2), 29.3 (CH_2), 28.6 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 18.8 ($C_{34}CH_3$), 18.2 ($C_{35}CH_3$), 14.1 (*C*-32); IR (film): ν_{max} (minor) = 3442 (br, O-H), 2921, 2845 cm^{-1} (C-H); ES-MS: m/z (minor): calcd for $C_{37}H_{64}O_7Na$: 643.4550; found: 643.4539.

(12*R*,15*S*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(propan-16-onyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (44): A solution of dimethyl sulfoxide (63 μL, 0.89 mmol) in dichloromethane (2 mL) was added dropwise through a syringe to a vigorously stirred solution of oxalyl chloride (71 μL, 0.81 mmol) in dichloromethane (2 mL) at −78 °C. After 30 min at −78 °C a solution of **42** and **43** (250 mg, 0.41 mmol) in dichloromethane (2 mL) was added dropwise via syringe and the temperature was maintained at −78 °C for a further 30 min, then triethylamine (0.34 mL, 2.43 mmol) was added dropwise through a syringe. The reaction warmed to rt over 1 h, and then was diluted with diethyl ether (100 mL), washed with phosphate buffer solution (pH 7.2, 50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (3:1) to afforded ketone **44** (200 mg, 80 %) as an oil. R_f = 0.57 (petroleum ether/diethyl ether 1:2); $[\alpha]_{29}^{D}$ = −58 (c = 0.99 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.34 – 7.32 (m, 4H; Ph), 7.28 – 7.25 (m, 1H; Ph), 4.50 (s, 2H; PhCH_2), 4.36 (t, J = 7.7 Hz, 1H; *H*-15), 4.06 – 4.02 (m, 2H; *H*-12, *H*-20), 3.52 – 3.46 (m, 2H; H_2-9), 3.43 (dt, J = 11.7, 3.3 Hz, 1H; *H*-19), 3.26 (s, 3H; $C_{34}OCH_3$), 3.23 (s, 3H; $C_{35}OCH_3$), 2.83 – 2.72 (m, 2H; H_2-17), 2.25 – 2.15 (m, 2H; *H*-14, *H*-18), 2.14 – 1.97 (m, 1H; *H*-13), 1.92 – 1.85 (m, 1H; *H*-14), 1.83 – 1.48 (m, 7H; H_2-10, H_2-11, *H*-13, *H*-18, *H*-21), 1.40 – 1.34 (m, 1H; *H*-21), 1.34 – 1.21 (m, 20H; H_2-22 → H_2-31), 1.28 (s, 3H; $C_{34}CH_3$), 1.26 (s, 3H; $C_{35}CH_3$), 0.88 (t, J = 6.8 Hz, 3H; H_3-32); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 212.9 (*C*=O), 138.6 (*ipso* *C*-C), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 99.7 (*C*-34), 98.8 (*C*-35), 83.2 (*C*-15), 80.7 (*C*-12), 73.7 (*C*-19), 72.9 (PhCH_2), 70.2 (*C*-9), 68.7 (*C*-20), 49.5 ($C_{35}OCH_3$), 47.8 ($C_{34}OCH_3$), 34.8 (*C*-17), 32.1 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.6 (6 × CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 21.6 (CH_2), 18.8 ($C_{34}CH_3$), 18.1 ($C_{35}CH_3$), 14.1 (*C*-32); IR (film): ν_{max} = 2925, 2853 (C-H), 1714 cm^{-1} (C=O); ES-MS: m/z: calcd for $C_{37}H_{62}O_7Na$: 641.4393; found: 641.4334.

(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxypropyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (43) and **(12*R*,15*S*,16*R*,19*R*,20*S*,34*R*,35*R*)-34,35-dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-hydroxypropyl)-tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (42)**: L-Selectride (1.0 M in THF, 0.64 mL, 0.64 mmol) was added dropwise through a syringe to a vigorously stirred solution of **44** (200 mg, 0.330 mmol) in THF (6.4 mL) at −100 °C. After 10 min at −100 °C, methanol (1 mL) was added dropwise through a syringe, then the reaction mixture was warmed to rt, and passed through a small pad of silica eluting with diethyl ether. Concentration in vacuo, then purification by flash column chromatography eluting with petroleum ether/diethyl ether (2:3) afforded alcohol **43** (140 mg, 70 %), as an oil, along with a mixture of alcohols **42** and **43** (55 mg, 27 %) also as an oil. The diastereoisomeric ratio (**43**/**42** 4:1) was assigned by integration of the peaks at δ_H (major) = 3.28 (s, 3H; $C_{34}OCH_3$) and δ_H (minor) = 3.31 (s, 3H; $C_{34}OCH_3$) in the crude ^{1}H NMR. All data for the major and minor epimers was identical to that previously obtained for **43** and **42** respectively.

(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-benzyloxypropyl)-15-(16-*tert*-butyldimethylsilyloxypropyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (45): TBSCl (110 mg, 0.73 mmol) was added in one portion to a solution of **43** (90 mg, 0.145 mmol) and imidazole (70 mg, 1.01 mmol) in DMF (0.6 mL). After heating at 45 °C for 14 h, the reaction mixture was diluted with diethyl ether (100 mL), washed with phosphate buffer solution (pH 7.2, 40 mL) and saturated NaCl solution (40 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (5:1 → 1:1) afforded TBS ether **45** (92 mg, 87 %) as an oil. R_f = 0.54 (petroleum ether/diethyl ether 1:1); $[\alpha]_{29}^{D}$ = −36 (c = 0.50 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.35 – 7.31 (m, 4H; Ph), 7.29 – 7.26 (m, 1H; Ph), 4.50 (s, 2H; PhCH_2), 4.06 – 4.04 (m, 1H; *H*-20), 3.91 – 3.86 (m, 2H; *H*-12, *H*-15), 3.57 – 3.54 (m, 1H; *H*-16), 3.51 – 3.43 (m, 3H; H_2-9, *H*-19), 3.28 (s, 3H; $C_{34}OCH_3$), 3.23 (s, 3H; $C_{35}OCH_3$), 1.99 – 1.95 (m, 1H; *H*-14), 1.94 – 1.84 (m, 3H; *H*-14, *H*-17, *H*-18), 1.76 – 1.44 (m, 8H; H_2-10, H_2-11, H_2-13, *H*-18, *H*-21), 1.33 – 1.22 (m, 22H; *H*-17, *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.26 (s, 3H; $C_{35}CH_3$), 0.88 – 0.86 (m, 12H; H_3-32, C(CH_3)$_3$), 0.08 (s, 3H; SiCH_3), 0.05 (s, 3H; SiCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.7 (*ipso* *C*-C), 128.3 (Ph), 127.6 (Ph), 127.4 (Ph), 99.6 (*C*-34), 98.7 (*C*-35), 81.7 (*C*-15), 79.0 (*C*-12), 75.8 (*C*-16), 75.4 (*C*-19), 72.8 (PhCH_2), 70.4 (*C*-9), 68.9 (*C*-20), 49.6 ($C_{35}OCH_3$), 47.7 ($C_{34}OCH_3$), 32.4 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 29.7 (CH_2), 29.6 (4 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 26.0 (C(CH_3)$_3$), 25.7 (CH_2), 22.7 (CH_2), 18.8 ($C_{34}CH_3$), 18.2 ($C_{35}CH_3$) 18.2 (C(CH_3)$_3$), 14.1 (*C*-32), −4.1 (SiCH_3), −4.7 (SiCH_3); IR (film): ν_{max} = 2924, 2853 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{43}H_{78}O_7Si$: C 70.3, H 10.69; found: C 70.5, H 10.48.

(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(9-hydroxypropyl)-15-(16-*tert*-butyldimethylsilyloxypropyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (46): Ethanol (7 mL) was added to a mixture of **45** (100 mg, 0.136 mmol) and palladium hydroxide (20 mg, 20 %), and the reaction placed under a hydrogen atmosphere. After 12 h at rt, the reaction mixture was passed through a small pad of Celite and concentrated in vacuo to afford alcohol **46** (82 mg, 94 %), as an oil, which was used in the subsequent step without further purification. R_f = 0.44 (petroleum ether/diethyl ether 1:2); $[\alpha]_{29}^{D}$ = −44 (c = 0.65 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 4.06 – 4.03 (m, 1H; *H*-20), 3.97 – 3.93 (m, 2H; *H*-12, *H*-15), 3.68 – 3.61 (m, 2H; H_2-9), 3.61 – 3.56 (m, 1H; *H*-16), 3.47 – 3.43 (m, 1H; *H*-19), 3.28 (s, 3H; $C_{34}OCH_3$), 3.24 (s, 3H; $C_{35}OCH_3$), 2.14 (br s, 1H; O*H*), 2.01 – 1.96 (m, 1H; *H*-13), 1.96 – 1.84 (m, 3H; *H*-14, *H*-17, *H*-18), 1.73 – 1.46 (m, 8H; H_2-10, H_2-11, *H*-13, *H*-14, *H*-18, *H*-21), 1.33 – 1.23 (m, 22H; *H*-17, *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.26 (s, 3H; $C_{35}CH_3$), 0.88 – 0.86 (m, 12H; H_3-32, C(CH_3)$_3$), 0.07 (s, 3H; SiCH_3), 0.06 (s, 3H; SiCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 99.6 (*C*-34), 98.7 (*C*-35), 81.5 (*C*-15), 79.4 (*C*-12), 75.4 (*C*-16), 75.3 (*C*-19), 68.9 (*C*-20, 62.9 (*C*-9), 49.6 ($C_{35}OCH_3$), 47.7 ($C_{34}OCH_3$), 32.5 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 30.7 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (4 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 26.0 (C(CH_3)$_3$), 25.9 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 18.8 ($C_{34}CH_3$), 18.2 ($C_{35}CH_3$) 18.2 (C(CH_3)$_3$), 14.1 (*C*-32), −4.1 (SiCH_3), −4.6 (SiCH_3); ES-MS: m/z: calcd for $C_{36}H_{72}O_7SiNa$: 667.4945; found: 667.4966.

(12*R*,15*S*,16*S*,19*R*,20*S*,34*R*,35*R*)-34,35-Dimethoxy-34,35-dimethyl-19-(12-(but-9-ynyl)-15-(16-*tert*-butyldimethylsilyloxypropyl)tetrahydrofuran)-20-dodecanyl-[33,36]-dioxane (47)

1) Oxidation of 46 to the aldehyde: Dess – Martin periodinane (33 mg, 0.078 mmol) was added in one portion to a solution of **46** (25 mg, 0.039 mmol) and pyridine (17 mL, 0.23 mmol) in dichloromethane (1 mL) at 0 °C. The resulting suspension was stirred for 3 h at 0 °C, then diluted with dichloromethane (25 mL) and poured onto a mixture of sodium thiosulfate solution (20 %, 4 mL) and saturated sodium bicarbonate solution (4 mL). The organic phase was separated, and the aqueous phase re-extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Filtration through a short pad of silica gel eluting with petroleum ether/diethyl ether (2:1) afforded the aldehyde (24 mg, 96 %) as an oil. R_f = 0.47 (petroleum ether/diethyl ether 1:2); $[\alpha]_{29}^{D}$ = −42 (c = 0.92 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 9.77 (br s, 1H; *H*-9), 4.06 – 4.03 (m, 1H; *H*-20), 3.96 – 3.89 (m, 1H; *H*-12), 3.88 (q, J = 7.0 Hz, 1H; *H*-15), 3.56 – 3.51 (m, 1H; *H*-16), 3.46 – 3.41 (m, 1H; *H*-19), 3.27 (s, 3H; $C_{34}OCH_3$), 3.23 (s, 3H; $C_{35}OCH_3$), 2.60 – 2.40 (m, 2H; H_2-10), 2.03 – 1.74 (m, 5H; H_2-11, *H*-13, *H*-14, *H*-18), 1.74 – 1.55 (m, 2H; *H*-14, *H*-18), 1.54 – 1.40 (m, 3H; *H*-13, *H*-17, *H*-21), 1.33 – 1.19 (m, 22H; *H*-17, *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.26 (s, 3H; $C_{35}CH_3$), 0.88 – 0.86 (m, 12H; H_3-32, C(CH_3)$_3$), 0.07 (s, 3H; SiCH_3), 0.05 (s, 3H; SiCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 202.1 (*C*-9), 99.7 (*C*-34), 98.7 (*C*-35), 81.9 (*C*-15), 78.1 (*C*-12), 75.7 (*C*-16), 75.4 (*C*-19), 68.9 (*C*-20), 49.6 ($C_{35}OCH_3$), 47.7 ($C_{34}OCH_3$), 40.8 (*C*-10), 32.5 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 29.6 (3 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.0 (C(CH_3)$_3$), 25.9 (CH_2), 22.7 (CH_2), 18.8

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($C_{34}CH_3$), 18.2 ($C_{35}CH_3$) 18.2 ($C(CH_3)_3$), 14.1 (*C*-32), −4.1 (SiCH_3), −4.6 (SiCH_3); IR (film): ν_{max} = 2927, 2854 (C-H), 2780 (H-C=O), 1728 cm^{-1} (HC=O); ES-MS: *m*/*z*: calcd for $C_{36}H_{70}O_7SiNa$: 665.4783; found: 665.4765.

2) Homologation to the terminal alkyne: Diethyl(diazomethyl)phosphonate (6.2 mg, 0.041 mmol) in THF (0.2 mL) was added dropwise to a slurry of potassium *tert*-butoxide (4.6 mg, 0.041 mmol) in THF (0.2 mL) at −78 °C. After 10 min at −78 °C, a pale yellow colour was observed to form, and a solution of the above aldehyde (22mg, 0.034 mmol) in THF (0.5 mL) was added dropwise through a syringe. On addition of the aldehyde the solution turned a bright yellow colour and was left to stir at −78 °C for 16 h, before being warmed to rt and stirred for a further 4 h. After this period, water (1 mL) was added, and the reaction mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether/diethyl ether (6:1 → 3:1) afforded alkyne **47** (16.6 mg, 76%) as an oil. R_f = 0.40 (petroleum ether/diethyl ether 4:1); $[\alpha]_{29}^{D}$ = −39 (*c* = 0.65 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 4.07–4.03 (m, 1H; *H*-20), 4.03–3.96 (m, 1H; *H*-12), 3.89 (dt, *J* = 8.2, 6.4 Hz, 1H; *H*-15), 3.59–3.54 (m, 1H; *H*-16), 3.44 (dt, *J* = 6.8, 4.0 Hz, 1H; *H*-19), 3.29 (s, 3H; $C_{34}OCH_3$), 3.23 (s, 3H; $C_{35}OCH_3$), 2.32–2.22 (m, 2H; H_2-10), 2.04–1.96 (m, 1H; *H*-13), 1.95–1.82 (m, 3H; *H*-14, *H*-17, *H*-18), 1.92 (t, 1H; *J* = 2.5, *H*-8), 1.76–1.59 (m, 4H; H_2-11, *H*-14, *H*-18), 1.55–1.41 (m, 2H; *H*-13, *H*-21), 1.33–1.18 (m, 22H; *H*-17, *H*-21, H_2-22 → H_2-31), 1.29 (s, 3H; $C_{34}CH_3$), 1.26 (s, 3H; $C_{35}CH_3$), 0.88–0.86 (m, 12H; H_3-32, $C(CH_3)_3$), 0.08 (s, 3H; $SiCH_3$), 0.06 (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 99.7 (*C*-34), 98.7 (*C*-35), 84.3 (*C*-9), 81.8 (*C*-15), 77.8 (*C*-12), 75.8 (*C*-16), 75.4 (*C*-19), 68.9 (*C*-20), 68.2 (*C*-8), 49.6 ($C_{35}OCH_3$), 47.7 ($C_{34}OCH_3$), 34.6 (*C*-11), 32.2 (*C*-13), 31.9 (CH_2), 31.6 (CH_2), 30.8 (*C*-17), 29.7 (CH_2), 29.6 (4 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (*C*-14), 26.0 ($C(CH_3)_3$), 26.0 (CH_2), 25.7 (*C*-18), 22.7 (CH_2), 18.8 ($C_{34}CH_3$), 18.2 ($C_{35}CH_3$) 18.2 ($C(CH_3)_3$), 15.6 (*C*-10), 14.1 (*C*-32), −4.1 (SiCH_3), −4.7 (SiCH_3); IR (film): ν_{max} = 3315 (C≡C-H), 2926, 2855 (C-H), 2118 cm^{-1} (C≡C); ES-MS: *m*/*z*: calcd for $C_{37}H_{70}O_6SiNa$: 661.4834; found: 661.4817.

(*E*/*Z*)-(4*R*,12*R*,15*S*,16*S*,19*R*,20*S*,34*S*)-4,16-di-*tert*-Butyldimethylsilyloxy-19,20-butanediacetal-6-en-8-yne-muricatetrocin C (48): A solution of **47** (15.5 mg, 0.024 mmol) in triethylamine (0.6 mL) was added dropwise through a syringe to a solution of **5** (15.0 mg, 0.036 mmol), copper iodide (2.0 mg, 0.010mmol) and $[PdCl_2(PPh_3)_2]$ (1.5 mg, 0.002 mmol) in triethylamine at rt. After 3 h at rt, all volatiles were removed in vacuo. Purification by flash column chromatography eluting with dichloromethane/diethyl ether (100:0 → 95:5) afforded enyne **48** (18.0 mg, 81%), an oil, as an inseparable mixture of olefin isomers [*E*/*Z*, 7.5:1; assigned by integration of the peaks at δ_H (major) = 6.02 (dt, *J* = 15.8, 7.7 Hz, 1H; *H*-6) and δ_H (minor) = 5.89 (dt, J = 10.8, 7.4 Hz, 1H; *H*-6). R_f = 0.20 (dichloromethane/diethyl ether 95:5); $[\alpha]_{29}^{D}$ = −27 (*c* = 0.60 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ (major) = 7.09 (br s, 1H; *H*-33), 6.02 (dt, *J* = 15.8, 7.7 Hz, 1H; *H*-6), 5.47 (d, *J* = 15.8 Hz, 1H; *H*-7), 5.00 (br q, *J* = 6.3 Hz, 1H; *H*-34), 4.07–4.01 (m, 2H; *H*-20, *H*-4), 4.00–3.92 (m, 1H; *H*-12), 3.88 (dt, *J* = 7.9, 6.4 Hz, 1H; *H*-15), 3.58–3.51 (m, 1H; *H*-16), 3.45–3.41 (m, 1H; *H*-19), 3.28 (s, 3H; BDA-OCH_3), 3.23 (s, 3H; BDA-OCH_3), 2.42 (d, *J* = 5.7 Hz, 2H; H_2-3), 2.39–2.30 (m, 2H; H_2-10), 2.29–2.21 (m, 2H; H_2-5), 2.04–1.97 (m, 1H; *H*-13), 1.95–1.81 (m, 3H; *H*-14, *H*-17, *H*-18), 1.76–1.60 (m, 4H; H_2-11, *H*-14, *H*-18), 1.55–1.44 (m, 2H; *H*-13, *H*-21), 1.41 (d, *J* = 6.8 Hz, 3H; H_3-35), 1.29 (s, 3H; BDA-CCH_3), 1.28–1.23 (m, 25H; *H*-17, *H*-21, H_2-22 → H_2-31, BDA-CCH_3), 0.90–0.85 (m, 21H; H_3-32, 2 × $C(CH_3)_3$), 0.08 (s, 3H; $SiCH_3$), 0.06 (s, 6H; 2 × $SiCH_3$), 0.01 (s, 3H; $SiCH_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ (minor, selected peaks) = 7.13 (br s, 1H; *H*-33), 5.89 (dt, *J* = 10.8, 7.4 Hz, 1H; *H*-6), 5.54 (d, *J* = 10.8 Hz, 1H; *H*-7); ^{13}C NMR (100 MHz; $CDCl_3$): δ (major) = 173.7 (*C*-1), 151.7 (*C*-33), 138.2 (*C*-6), 130.7 (*C*-2), 112.9 (*C*-7), 99.7 (BDA-CO_2), 98.7 (BDA-CO_2), 89.0 (*C*-9), 81.8 (*C*-15), 79.1 (*C*-8), 78.0 (*C*-12), 77.5 (*C*-34), 75.9 (*C*-16), 75.4 (*C*-19), 69.3 (*C*-4), 68.9 (*C*-20), 49.6 (BDA-OCH_3), 47.7 (BDA-OCH_3), 40.8 (*C*-5), 35.0 (*C*-11), 32.8 (*C*-3), 32.2 (*C*-13), 31.9 (CH_2), 31.6 (CH_2), 30.9 (*C*-17), 29.7 (CH_2), 29.6 (4 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (*C*-14), 26.0 ($C(CH_3)_3$), 26.0 (CH_2), 25.8 ($C(CH_3)_3$), 25.7 (*C*-18), 22.7 (CH_2), 18.9 ($CHCH_3$), 18.8 (BDA-CCH_3), 18.3 ($C(CH_3)_3$), 18.2 (BDA-CCH_3), 18.0 ($C(CH_3)_3$), 16.6 (*C*-10), 14.1 (*C*-32), −4.0 (SiCH_3), −4.5 (SiCH_3), −4.6 (SiCH_3), −4.7 (SiCH_3); IR (film): ν_{max} = 2927, 2855 (C-H), 1760 (C=O), 1600 cm^{-1} (C=C); ES-MS: *m*/*z*: calcd for $C_{53}H_{96}O_9Si_2Na$: 955.6485; found: 955.6476.

(4*R*,12*R*,15*S*,16*S*,19*R*,20*S*,34*S*)-Muricatetrocin C (2)

1) Reduction of the enyne 48: Wilkinson's catalyst (3 mg, 0.0032 mmol) was added in one portion to a solution of **48** (15 mg, 0.016 mmol) in benzene/ethanol (1:1, 1 mL), and the reaction was placed under a hydrogen atmosphere. After 11 h at rt, all volatiles were removed in vacuo. Filtration through a short pad of silica gel eluting with petroleum ether/diethyl ether (3:1) afforded fully protected muricatetrocin C (11 mg, 76%) as an oil. R_f = 0.29 (petroleum ether/diethyl ether 2:1); $[\alpha]_{29}^{D}$ = −31 (*c* = 0.38 in CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.11 (br s, 1H; *H*-33), 5.02 (br q, *J* = 6.2 Hz, 1H; *H*-34), 4.06–4.03 (m, 1H; *H*-20), 3.95 (qn, *J* = 5.4 Hz, 1H; *H*-4), 3.89 (dt, *J* = 7.6, 6.5 Hz, 1H; *H*-15), 3.87–3.82 (m, 1H; *H*-12), 3.53–3.58 (m, 1H; *H*-16), 3.46–4.42 (m, 1H; *H*-19), 3.28 (s, 3H; BDA-OCH_3), 3.23 (s, 3H; BDA-OCH_3), 2.42 (d, *J* = 5.4 Hz, 2H; H_2-3), 2.00–1.93 (m, 1H; *H*-13), 1.93–1.83 (m, 3H; *H*-14, *H*-17, *H*-18), 1.72–1.65 (m, 1H; *H*-18), 1.65–1.59 (m, 1H; *H*-14), 1.55–1.47 (m, 2H; *H*-13, *H*-21), 1.46–1.36 (m, 4H; H_2-5, H_2-11), 1.41 (d, *J* = 6.8 Hz, 3H; H_3-35), 1.33–1.19 (m, 32H; *H*-17, *H*-21, H_2-6 → H_2-10, H_2-22 → H_2-31), 1.29 (s, 3H; BDA-CCH_3), 1.26 (s, 3H; BDA-CCH_3), 0.89–0.84 (m, 21H; H_3-32, 2 × $C(CH_3)_3$), 0.08 (s, 3H; $SiCH_3$), 0.05 (s, 6H; 2 × $SiCH_3$), 0.02 (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 174.0 (*C*-1), 151.4 (*C*-33), 130.9 (*C*-2), 99.7 (BDA-CO_2), 98.7 (BDA-CO_2), 81.6 (*C*-15), 79.4 (*C*-12), 77.4 (*C*-34), 75.8 (*C*-16), 75.4 (*C*-19), 70.2 (*C*-4), 68.9 (*C*-20), 49.6 (BDA-OCH_3), 47.7 (BDA-OCH_3), 36.9 (*C*-5), 35.9 (*C*-11), 32.7 (*C*-3), 32.4 (*C*-13), 31.9 (CH_2), 31.6 (CH_2), 30.9 (*C*-17), 29.7 (2 × CH_2), 29.6 (5 × CH_2), 29.5 (2 × CH_2), 29.3 (CH_2), 27.8 (*C*-14), 26.3 (CH_2), 26.0 ($C(CH_3)_3$), 26.0 (CH_2), 25.8 ($C(CH_3)_3$), 25.7 (*C*-18), 25.1 (CH_2), 22.6 (CH_2), 18.9 ($CHCH_3$), 18.8 (BDA-CCH_3), 18.2 ($C(CH_3)_3$), 18.2 (BDA-CCH_3), 18.0 ($C(CH_3)_3$), 14.1 (*C*-32), −4.0 (SiCH_3), −4.5 (SiCH_3), −4.5 (SiCH_3), −4.7 (SiCH_3); IR (film): ν_{max} = 2928, 2855 (C-H), 1760 cm^{-1} (C=O); ES-MS: *m*/*z*: $C_{53}H_{102}O_9Si_2Na$: 961.6955; found: 961.6970.

2) Global deprotection: Trifluoroacetic acid/water (9:1, 0.5 mL) was added in one portion to fully protected **2** (8.0 mg, 0.0085 mmol). The solution was swirled manually for 30 s, then all volatiles were removed in vacuo. This process was repeated then purification by flash column chromatography eluting with chloroform/methanol (99:1 → 96:4) afforded muricatetrocin C (**2**; 4.2 mg, 82%) as a white amorphous solid. M.p. 65–67 °C (m.p. 65–66 °C)[5]; R_f = 0.08 (EtOAc); $[\alpha]_{29}^{D}$ = +5.8 (*c* = 0.38 in CH_2Cl_2), $[\alpha]_{29}^{D}$ = +6.3 (in CH_2Cl_2)[5]; ^{1}H NMR (600 MHz; $CDCl_3$): δ = 7.18 (d, *J* = 1.1 Hz, 1H; *H*-33), 5.06 (qd, *J* = 6.8, 1.1 Hz, 1H; *H*-34), 3.89–3.87 (m, 1H; *H*-12), 3.87–3.83 (m, 1H; *H*-4), 3.82 (q, 1H; *J* = 7.2, *H*-15), 3.63–3.60 (m, 2H; *H*-19, *H*-20), 3.47–3.43 (m, 1H; *H*-16), 2.90 (br s, 2H; O*H*), 2.53 (dt, *J* = 15.1, 1.6 Hz, 1H; *H*-3), 2.40 (dd, *J* = 15.1, 8.3 Hz, 1H; *H*-3), 2.04–2.01 (m, 1H; *H*-13), 2.00–1.97 (m, 1H; *H*-14), 1.70–1.40 (m, 6H; H_2-17, H_2-18, H_2-21), 1.60–1.40 (m, 3H; H_2-11, *H*-13), 1.62–1.55 (m, 1H; *H*-14) 1.50–1.40 (m, 2H; H_2-5), 1.43 (d, *J* = 6.8 Hz, 3H; H_3-35), 1.40–1.20 (m, 32H; H_2-6 → H_2-10, H_2-22 → H_2-31, 2 × O*H*), 0.88 (t, *J* = 6.9 Hz, 3H; H_3-32); ^{13}C NMR (150 MHz; $CDCl_3$): δ = 174.5 (*C*-1), 151.7 (*C*-33), 131.2 (*C*-2), 81.7 (*C*-15), 79.3 (*C*-12), 77.9 (*C*-34), 74.7, 74.4 (*C*-20, *C*-19), 74.3 (*C*-16), 70.0 (*C*-4), 37.4 (*C*-5), 33.5–22.7 (*C*-6 → *C*-11, *C*-17, *C*-18, *C*-21 → *C*-31), 33.4 (*C*-3), 32.4 (*C*-13), 28.4 (*C*-14), 19.1 (*C*-35), 14.1 (*C*-32); IR (film: ν_{max} = 3422 (br, O-H), 2928, 2855 (C-H), 1733 (C=O), 1675 cm^{-1} (C=C); FAB-MS: *m*/*z* (%): calcd for $C_{35}H_{64}O_7Na$: 619.4544; found: 619.4522; EI-MS: *m*/*z* (%): 597.6 (100) $[M]^+$, 525.81 (25) $[M - C_2H_4O - CO]^+$.

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