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The Synthesis of Azadirachtin: A Potent Insect Antifeedant

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Abstract: We describe in full the first synthesis of the potent insect antifeedant azadirachtin through a highly convergent approach. An *O*-alkylation reaction is used to unite decalin ketone and propargylic mesylate fragments, after which a Claisen rearrangement constructs the central C8–C14 bond in a stereoselective fashion. The allene which results from this sequence then enables a second critical carbon–carbon bond forming event whereby the [3.2.1] bicyclic system, present in the natural product, is generated via a 5-*exo*-radical cyclisation process. Finally, using knowledge gained through our early studies into the reactivity of the natural product, a series of carefully designed steps completes the synthesis of this challenging molecule.

Keywords: azadirachtin · Claisen rearrangement · epoxidation · natural products · total synthesis

Introduction

Azadirachtin (**1**) is a C-*seco* limonoid that was first isolated from the Indian neem tree *Azadirachta indica* in 1968 (Figure 1).[1] It has since been the subject of intensive research owing to its impressive biological activity:[2–11] most notably antifeedant and growth disrupting effects against a broad spectrum of insect species (>200). Moreover, **1** possesses no significant toxicity towards higher organisms.[12] In addition to the wide-ranging biological properties of **1**, its unique molecular architecture has attracted considerable attention. Indeed, the precise chemical structure of **1** was only determined some 17 years after its isolation following extensive studies within our group[13,14] and others.[15–18]

Azadirachtin constitutes an exceptionally challenging synthesis target, possessing 16 contiguous stereogenic centres, seven of which are tetrasubstituted. The molecular frame-

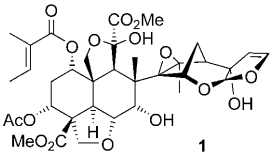

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Figure 1. Azadirachtin **1**.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801103: Experimental details for the preparation of compounds: **5**, **16**–**18**, **21**, **25**, **26**, **30**, **31**, **37**, **50**–**56**, **64**, **66**–**68**, **70**, **73**, **84**, **84a**.

work of **1** is also richly-decorated: its 16 oxygen atoms are contained within a variety of functional groups including an ether, an enol ether, both acetal and hemi-acetal moieties, three distinct ester groups, two hydroxyl groups and a tetra-substituted epoxide. Furthermore, in solution the natural product maintains a highly rigid conformation owing to hydrogen bonds between the ether at C6 and the hydroxyl groups at C7 and C20 as well as between the C11 hemi-acetal and the C13–C14 epoxide (Figure 2).[13] Other hydrogen-bonding arrangements have also been reported for certain crystalline forms of the natural product.[18]

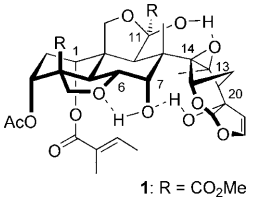


Figure 2. Numbering and hydrogen-bonding pattern present in azadirachtin **1**.[13]

Given our long-standing interest in the preparation of insect antifeedants,[19–21] azadirachtin (**1**) represented an irresistible synthesis target[22] which has also attracted the attention of many other research groups around the world.[23–46]

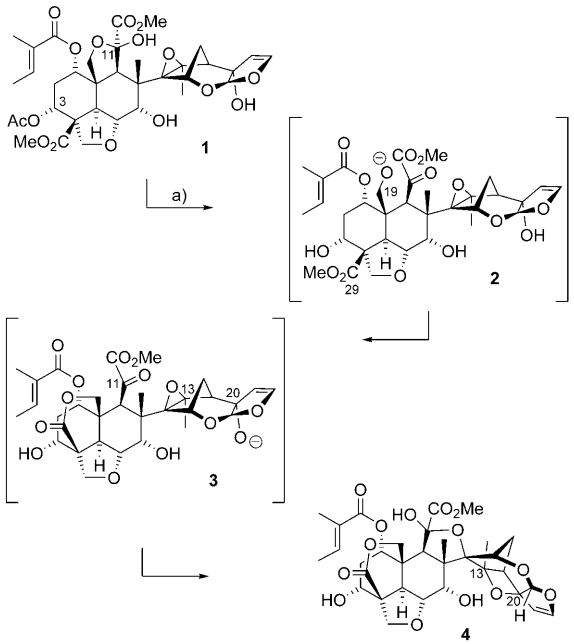
Results and Discussion

At the outset of the programme, we thought it pertinent to investigate the general reactivity profile of azadirachtin, as this knowledge would be important in the development of a synthesis plan. Preliminary studies indicated that azadirachtin was highly unstable under basic conditions.[47] For example, exposure of **1** to sodium methoxide in methanol leads to deprotonation of its C11 hemiacetal, resulting in an equilibrium between open (**2**) and closed forms (Scheme 1). In the open form, the C19 alkoxide in **2** is intercepted by an intramolecular transesterification at C29 to form a bridging [3.3.1] lactone ring system (**3**). A further rearrangement then occurs, whereby the C20 alkoxide in **3** opens the oxirane ring at the C13 position and the resultant hydroxyl group attacks the newly formed carbonyl at C11. Saponification of the C3 acetate is also observed, generating the oxetane **4** as the major isolable product.[47]

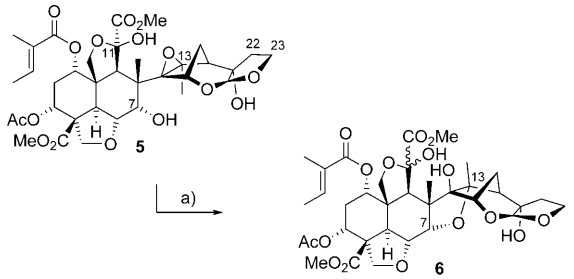
Similarly, azadirachtin was shown to be unstable under acidic conditions, mainly (but not exclusively) due to the presence of the enol ether feature at C22–C23. However, even in the absence of this functional group, instability was still encountered. Treating 22,23-dihydroazadirachtin (**5**) with the acidic resin, Amberlyst-15, promotes an irreversible ring-opening of the epoxide at C13 by the proximal C7 hydroxyl group, while also effecting equilibration at the C11 hemi-acetal centre to give **6** (Scheme 2).[48]

These early observations proved critical as they clearly demonstrated that all the reactive functionality present in azadirachtin would need to be very carefully masked until the later stages of the synthesis programme.

Synthesis strategy: In pursuit of azadirachtin, we originally devised a highly convergent route involving direct coupling



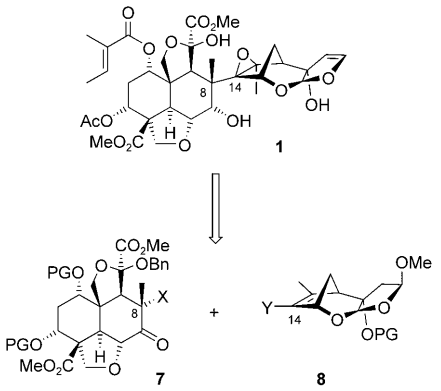
Scheme 1. Base-mediated rearrangement of azadirachtin **1**. a) NaOMe, MeOH, RT, 2.5 h, 23 %.[47]



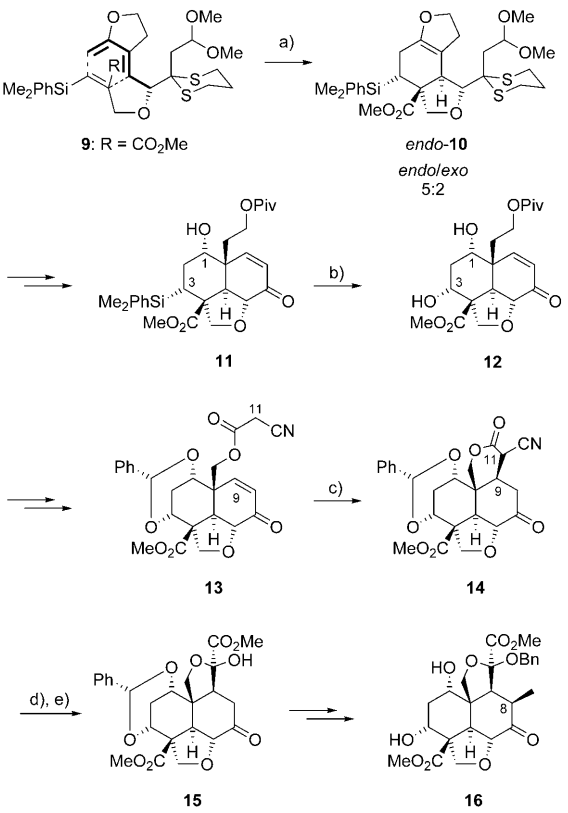
Scheme 2. Acid-mediated rearrangement of 22,23-dihydroazadirachtin (**5**). a) Amberlyst-15, 4 Å sieves, MeCN, RT, 3 d, 51 %.[48]

of two similarly sized fragments, **7** and **8**, to forge the central C8–C14 bond (Scheme 3). Whilst this disconnection made good strategic sense, it was recognised that such an approach would not be without its difficulties owing to the extreme steric congestion about this central linkage. Nonetheless, we were intrigued by the challenge and set about preparing appropriate coupling partners.

Decalin fragment synthesis: The first of these fragments, decalin **7**, has already been prepared in our group with various protecting group arrangements and is reported in full elsewhere.[49–51] Of particular note from this work is the use of an intramolecular Diels–Alder (IMDA) reaction, in which the judicious choice of a phenyldimethylsilyl group in triene **9** favours the desired *endo* product **10** in the cycloaddition process (Scheme 4). The silyl auxiliary also plays an important role in stereocontrol at the C1 position and ultimately reveals the requisite hydroxyl group at C3 following a Fleming–Tamao oxidation of **11**, accelerated by the use of



Scheme 3. Original synthesis plan. (PG = protecting group, Bn = benzyl).



Scheme 4. Highlights from our previously disclosed decalin fragment synthesis a) iPr$_2$NEt, hydroquinone, PhMe, 80 °C, 4 h, 57 %; b) Hg(CF$_3$CO$_2$)$_2$, TFA/AcOH 1:1, RT, 10 min, then AcOOH, 0 °C to RT, 2 h, 85 %; c) LiN(SiMe$_3$)$_2$, THF, 0 °C to RT, 70 min, 100 %; d) DMDO, acetone, 0 °C, 22 min; e) PPTS, MeOH, RT, 5.5 h, 70 % over 2 steps (Piv = pivaloyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, DMDO = dimethyldioxirane, PPTS = pyridinium *para*-toluenesulfonate).

mercuric bistrifluoroacetate.[52] Another interesting aspect of this synthesis is the use of a cyanoester-mediated conjugate addition in which the C9–C11 bond in **14** is constructed stereoselectively. Dimethyldioxirane (DMDO) oxidation of **14** and a novel methanolic ring contraction then provide access to the five-ring hemiacetal (**15**) observed in the natural product. Further steps yield a decalin fragment possessing the necessary methyl group at the C8-position (**16**).

While useful material was obtained from this total synthesis route, we also discovered an alternative preparation of the same decalin fragment (**16**) through degradation of azadirachtin itself (Scheme 5).[47,53,54] In the design of this degradative pathway, it was anticipated that the electron rich C20–C21 bond in azadirachtin (**1**) might undergo oxidative cleavage following appropriate masking of its most reactive functional groups (**1** → **17**). Indeed, treatment of **17** with pyridinium chlorochromate effected the expected oxidation of its C7 hydroxyl group and also achieved the required C20–C21 bond cleavage to give cyclic carbonate **18** in good yield. We then anticipated that **18** could undergo ring-opening with a suitable nucleophile, followed by deprotonation at C17, which in turn would lead to β-elimination of the neighbouring strained epoxide and retro-aldol reaction. This hypothesis proved correct and, when **18** was subjected to sodium methoxide in methanol, the expected reaction cascade proceeded smoothly in excellent yield to afford decalin **16**.

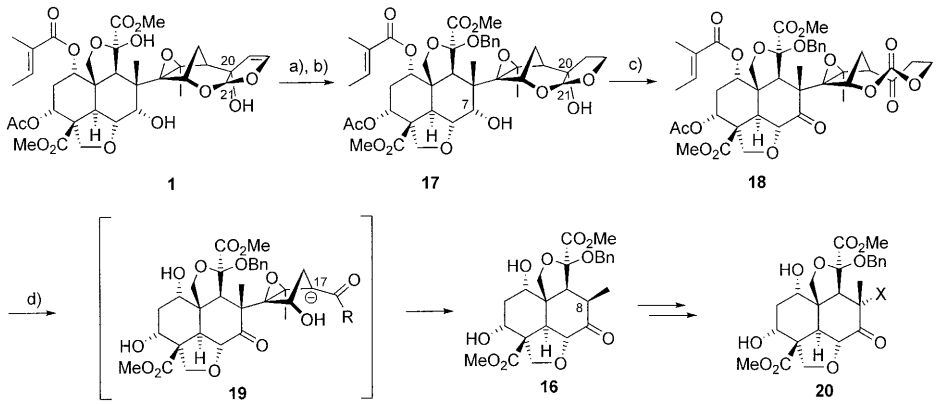
Formation of the hindered C8–C14 bond: We first proceeded to investigate the synthesis of a wide variety of hydroxyfuran acetal coupling partners,[22,55] broadly based around the structure of **8**, such that the pivotal C8–C14 bond-forming process could be examined in detail. Whilst it was clear that this coupling approach was ambitious, we were unprepared for the magnitude of problems that would be encountered during many years of endeavour. Model studies had provided encouragement for this critical carbon–carbon bond formation, yet the use of more complex coupling partners invariably met with failure.[56–59] The details of all these unprofitable studies and of all the various coupling partners investigated are not discussed here[60] as a new strategy emerged which eventually overcame all our problems.

In the revised strategy we chose to investigate a Claisen rearrangement to install the hindered C8–C14 bond in **1** as this process is well known to allow the formation of bonds between highly substituted centres.[61] Initial studies in this area were promising, allowing functionalisation of decalin **21**[62] via the intermediate enol ether **22**, which underwent a Claisen rearrangement to give **23** with exquisite diastereoselectivity (Scheme 6).[63]

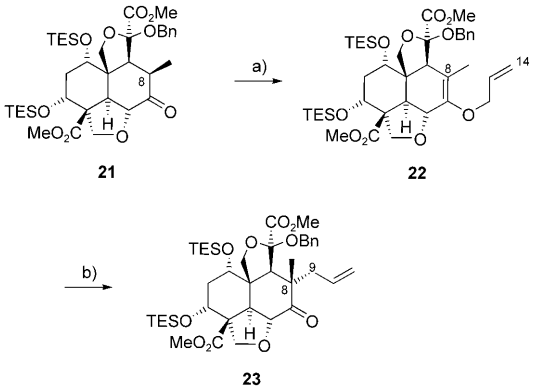
It is worthy of note that *C*-alkylation of **21** was not observed under the reaction conditions employed and this is believed to result primarily from steric constraints at the C8 position.[63]

We then proceeded to examine more complex model coupling partners, including allylic bromide **24** for which the *O*-alkylation reaction was similarly successful (**21** → **25**, Scheme 7). However, the stereochemical outcome in the Claisen rearrangement of **25** was disappointing and gave only the undesired diastereomer (**26**), which can not be progressed to azadirachtin.[64]

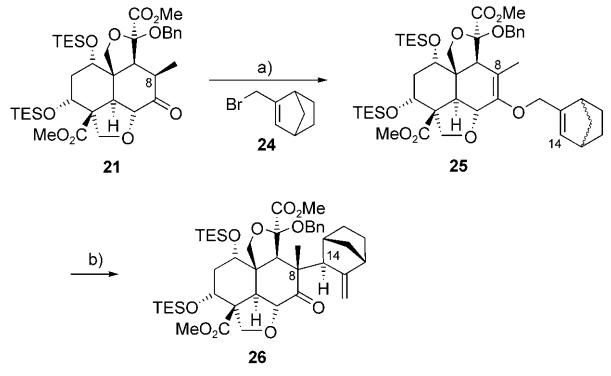
Once again we were forced to rethink our strategy and in the end a much improved concept was devised. Although a



Scheme 5. Transformation of azadirachtin **1** to decalin fragment **20**. a) H_2, Pd/C, MeOH, RT, 80 min, 69%; b) BnBr, Ag_2O, DMF, RT, 20 min, 62%; c) pyridinium chlorochromate, 4 Å sieves, CH_2Cl_2, 40°C, 1.5 h, 39%; d) NaOMe, MeOH, 0°C to RT, 2 h, 60% (DMF = *N*,*N*-dimethylformamide).

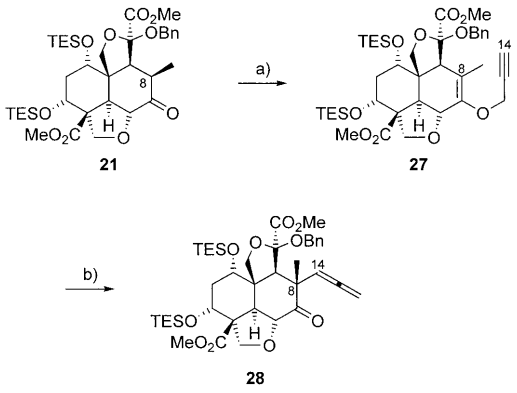


Scheme 6. Functionalisation at C8 via *O*-alkylation/allylic Claisen rearrangement. a) NaH, allyl bromide, [15]crown-5, THF, 0°C, 2 h, 66%; b) xylenes, reflux, 43 h, 71% ([15]crown-5 = 1,4,7,10,13-pentaoxacyclopentadecane, TES = triethylsilyl).



Scheme 7. Intramolecular C8–C14 bond formation via allylic Claisen rearrangement. a) NaH, [15]crown-5, **24**, THF, 0°C, 2 h, 96%; b) DCB, 167°C, 16 h, 42%, 83% based on conversion of one diastereomer (DCB = 1,2-dichlorobenzene).

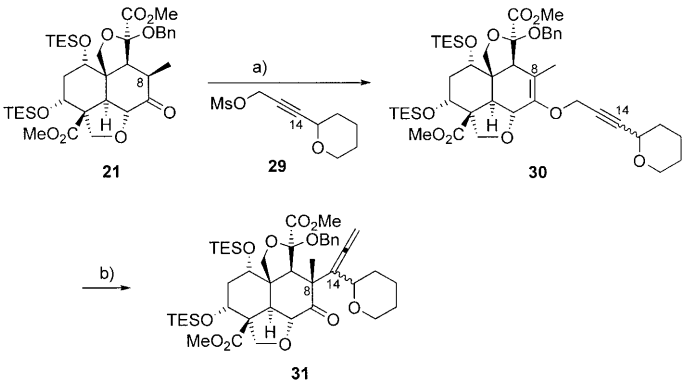
Claisen rearrangement could lead to the formation of a new carbon-carbon bond at C8, it became apparent that the steric constraints of a fully-functionalised hydroxyfuran acetal fragment would prohibit further profitable progression to the natural product. We therefore chose to employ a lesser-known, acetylenic variant of the Claisen rearrangement,[65] which would lead to a terminal allene motif. This particular feature would be highly versatile and amenable to further transformations which, in turn, could serve to construct the right hand portion of the natural product. In preparation therefore, we began by studying a simple propargylic Claisen rearrangement of the enol ether derivative **27** (Scheme 8). Pleasingly, upon heating in toluene to 145°C in a sealed tube, a quantitative rearrangement to allene **28** occurred after just two hours.[63]



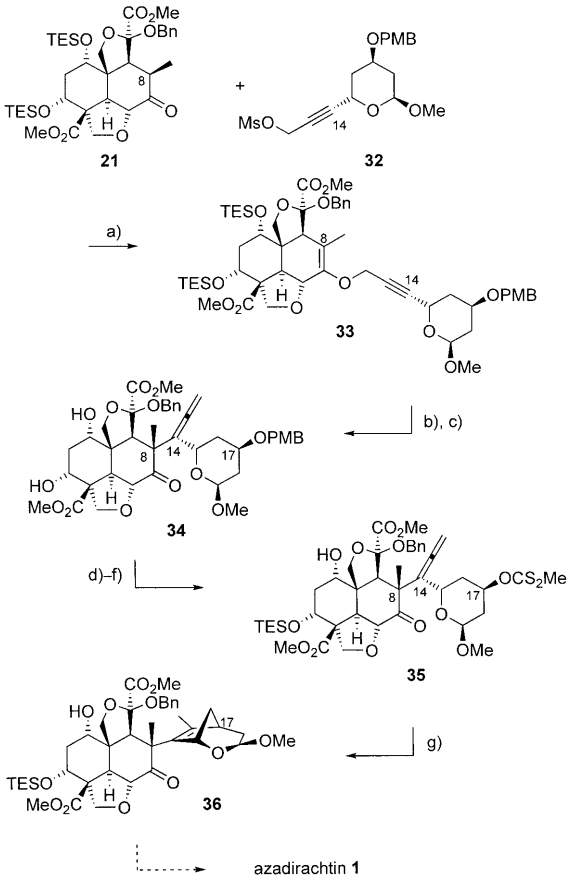
Scheme 8. Simple intramolecular C8-C14 bond formation via propargyl Claisen rearrangement. a) propargyl bromide, NaH, [15]crown-5, THF, 0°C, 4.5 h, 57%; b) PhMe, 145°C, sealed tube, 2 h, >98%.

Encouraged by this result, the approach was extended to the more complex propargylic mesylate **29** and again an *O*-alkylation/Claisen rearrangement sequence afforded the 1,1-disubstituted allene **31** (Scheme 9). In this instance, however, it was necessary to use higher temperatures and microwave heating to effect the desired transformation.[63]

We were then in a position to further progress this strategy, as it was envisaged that the initially formed allene could ultimately enable a further carbon–carbon bond-forming event. Gratifyingly, the coupling of fragments **21** and **32** proceeded without incident to generate propargyl enol ether **33** (Scheme 10). However, conditions could not be found to promote the Claisen rearrangement of **33**, despite extensive experimentation. It was proposed that this lack of reactivity was due to steric factors, as we had observed that hindered propargylic enol ethers required more forcing conditions to promote the desired rearrangement (cf. Schemes 8 and 9). As a consequence, the axial TES protecting groups present



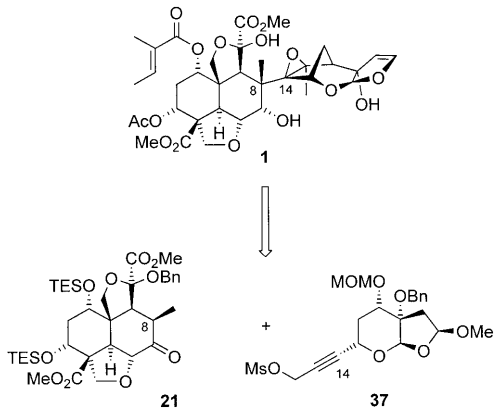
Scheme 9. Intramolecular C8–C14 bond formation via propargyl Claisen rearrangement. a) NaH, **29**, [15]crown-5, THF, 0 °C, 2 h, 66 %; b) DCB, microwave irradiation, 180 °C, 15 min then 220 °C, 15 min, 53 %.



Scheme 10. Studies towards **1**. a) NaH, [15]crown-5, THF, −78 °C, 8 h, 73 %; b) TBAF, THF, 0 °C, 2 h, 73 %; c) DCB, microwave irradiation, 180 °C, 15×1 min, 88 %; d) TES-OTf, iPr$_2$NEt, CH_2Cl_2, −78 °C, 15 min, 90 %; e) DDQ, CH_2Cl_2, H_2O, 0 °C, 2 h, 81 %; f) CS_2, NaH, MeI, THF −78 °C to 10 °C, 3.5 h, 87 %; g) Bu_3SnH, AIBN, PhMe, 110 °C, 4 h, 81 % (AIBN = azoisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyano-*para*-benzoquinone, Ms = methanesulfonate, PMB = *para*-methoxybenzyl, TBAF = tetra-*n*-butyl ammonium fluoride, Tf = trifluoromethanesulfonate).

in **33** were cleaved with a view to reducing steric effects in the transition state. To our delight, the reaction then proceeded in excellent yield to give allene **34** as a single diastereomer.

Careful consideration of the Claisen rearrangement product led us to propose that a C17-centred radical might undergo cyclisation onto the neighbouring allene and thus generate the [3.2.1] bicycle present in azadirachtin. Consequently, the *para*-methoxybenzyl ether at the C17 position of **34** was converted to the corresponding xanthate ester **35** using a series of straightforward steps. As predicted, when **35** was treated with AIBN and tributyltin hydride, a radical cyclisation occurred to generate a new carbon–carbon bond, thus establishing the requisite tricyclic framework in a single step (**36**).[66] Although intermediate **36** could in principle be converted to azadirachtin,[22,55] we instead opted for a bolder approach which would utilise a propargylic mesylate coupling partner containing all the requisite carbon atoms for the synthesis of the natural product (Scheme 11).[67]

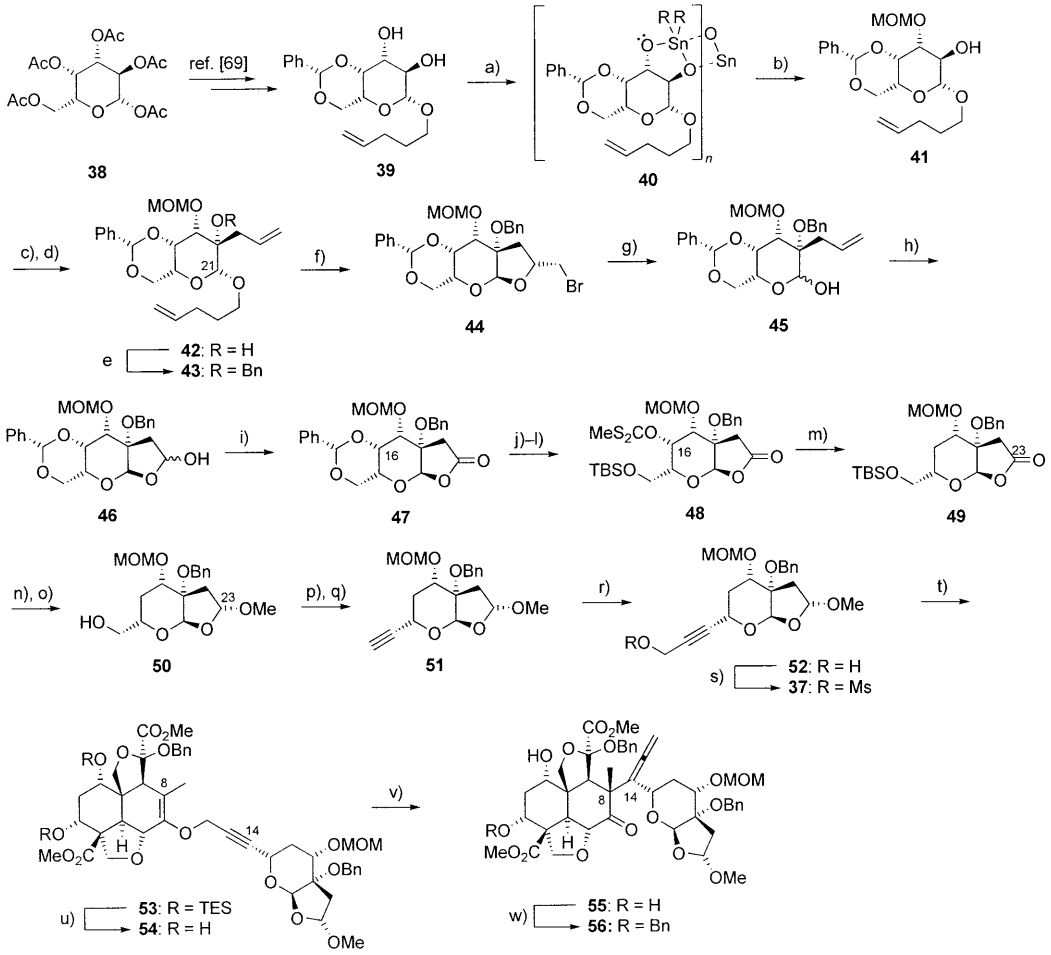


Scheme 11. Revised synthesis plan (MOM = methoxymethyl).

A fully functionalised propargylic mesylate: The route to propargylic mesylate **37**[68] began from a readily available carbohydrate source, namely β-D-galactose pentaacetate (**38**) which was converted to diol **39** in three steps (Scheme 12).[69]

Differentiation of this 1,2-diol was achieved by formation of the dimeric stannylidene acetal species **40**, thereby rendering the least hindered hydroxyl group unreactive and permitting selective formation of the desired methoxymethyl (MOM) ether (**41**, Scheme 12).[70] Parikh–Doehring oxidation of **41** was followed by a substrate controlled Grignard addition, in which the benzylidene acetal protecting group served to block the bottom face of the molecule providing **42** as a single diastereomer.[71] The tertiary alcohol present in **42** was then cleanly protected as its benzyl ether (**43**) under standard conditions.

In order to generate the tetrahydrofuran ring required for **37**, the C21 anomeric alcohol had first to be revealed by cleavage of the pentenyl protecting group in **43** (Scheme 12). Fraser-Reid reports the use of *N*-bromosuccinimide in wet acetonitrile to effect this type of transformation,[72] but in our case bromination of both alkenes present



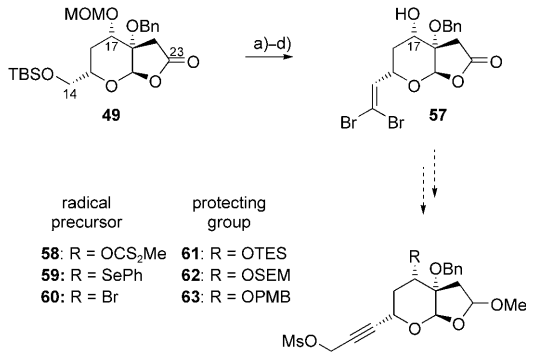
Scheme 12. MOM route. a) nBu$_2$SnO, MeOH, reflux, 2 h; b) MOMCl, 1,4-dioxane, 55 °C, 1.5 h, 93 % over 2 steps; c) iPr$_2$NEt, SO$_3$·pyridine, DMSO, 0 °C, 30 min; d) AllylMgCl, THF, −78 °C, 30 min, 85 % over 2 steps; e) NaH, BnBr, DMF, 0 °C, 18 h, 92 %; f) NBS, pH 7 buffer, MeCN, RT, 1.5 h, 58 % 1.4:1 mix of **44** and **45**; g) NH$_4$Cl, Zn, EtOH, reflux, 2 h; h) O$_3$, CH$_2$Cl$_2$, −78 °C, 15 min, then PS-PPh$_3$, −78 °C to RT, 18 h; i) nPr$_4$NRuO$_4$, NMO, MeCN, RT, 1 h, 76 % over 3 steps; j) TFA/H$_2$O/CH$_2$Cl$_2$ 1:1:20, RT, 97 %; k) TBSCl, DMAP, NEt$_3$, DMF, RT, 3 h, 71 %; l) CS$_2$, NaN(SiMe$_3$)$_2$, THF, −78 °C, 30 min, then MeI, −78 °C, 30 min, 92 %; m) AIBN, Bu$_3$SnH, PhMe, reflux, 2 h, >98 %; n) DIBAL-H, THF, −78 °C, 2 h, 91 %; o) CH(OMe)$_3$, CSA, MeOH, RT, 1 h, 82 % (3:1 23-α/β); p) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, then **50**, then NEt$_3$, −78 °C, 2.5 h; q) Ohira–Bestmann reagent, K$_2$CO$_3$, MeOH, RT, 16 h, 77 % over 2 steps; r) iPrMgCl, THF, 45 °C, then (CH$_2$O)$_n$, 45 °C, 2.5 h, 89 %; s) Ms$_2$O, iPr$_2$NEt, CH$_2$Cl$_2$, 0 °C, 1.5 h, 89 %; t) **21**, NaH, [15]crown-5, THF, 0 °C, 6 h, 65 %; u) TBAF, THF, RT, 16 h, 92 %; v) nitrobenzene, microwave irradiation, 185 °C, 3×5 min, >99 %; w) NaH, BnBr, nBuN$_4$I, THF, 60 °C, 16 h, 76 % (CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminiumhydride, DMAP = *N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethyl formamide, DMSO = dimethylsulfoxide, NBS = *N*-bromosuccinimide, NMO = *N*-methylmorpholine-*N*-oxide, Ohira-Bestmann reagent = dimethyl-(1-diazo-2-oxopropyl)phosphonate, PS = polystyrene supported, TBS = *tert*-butyldimethylsilyl).

in **43** was observed, resulting in an inseparable mixture of bromoalkane **44** and the desired lactol **45**. Fortunately, **45** could be obtained by treatment of bromoalkane **44** with activated zinc dust to effect a Boord elimination.[73,74] The δ-lactone **47** was then constructed by ozonolysis of the terminal olefin present in **45** followed by oxidation of the resultant bicyclic lactol with TPAP.[75] Our next task was the selective removal of the C16 hydroxyl group, which is absent in our target mesylate coupling fragment. Accordingly **47** was transformed in three steps to xanthate **48**, which then underwent smooth Barton–McCombie deoxygenation[76] to give **49**. Lactone **49** was subjected to a reduction/methanolysis sequence which led both to introduction of the C23 methyl acetal and to cleavage of the *tert*-butyldimethylsilyl (TBS) protecting group. Preparation of terminal alkyne **51** was subsequently achieved from **50** via Swern oxidation and treatment of the intermediate aldehyde with the Ohira–Bestmann reagent.[77] Finally, further homologation of **51** with paraformaldehyde was followed by mesylation to provide our coupling partner **37** in good overall yield.

Using the conditions developed during model studies, a successful coupling between propargylic mesylate **37** and decalin **21**[54] was achieved via an *O*-alkylation reaction to afford propargylic enol ether **53** (Scheme 12). Treating **53** with tetra-*n*-butylammonium fluoride (TBAF) then provided diol **54** in excellent yield, after which the crucial C8–C14 bond formation was effected by a microwave-induced Claisen rearrangement (**54** → **55**). However, our route again met with failure, when we attempted to selectively remove the C17 MOM protecting group: all conditions employed led to

significant decomposition owing to the presence of other acetals within the substrate (**56**).

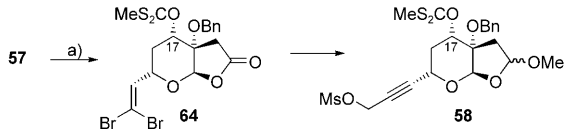
Alternatives to the C17 MOM ether: We therefore had to change the protecting group strategy for the pyran coupling partner such that the remaining steps in our synthesis could be achieved. Accordingly, several derivatives of the pyran fragment were targeted that utilised alternative functionality at C17, while only making minor adjustments to the synthesis route in place (**58**–**63**, Scheme 13). It was first necessary to find a suitable point in the synthesis of **37** at which selective cleavage of the C17 MOM ether could be carried out. We felt that it would not be feasible to remove this protecting group in the presence of either the C23 methyl acetal or the C14 TBS ether and so we chose to intercept the first generation route at intermediate **49** (Scheme 13). The TBS ether in **49** was readily cleaved under mild conditions and the resulting primary alcohol subjected to an oxidation/Wittig protocol to effect the necessary homologation. At this stage, we were able to selectively cleave the C17 MOM ether to provide the required secondary alcohol (**57**).



Scheme 13. Options for introducing a radical precursor at C17. a) TFA/H_2O/CH_2Cl_2 1:1:20, RT, 81%; b) *i*Pr_2NEt, SO_3·pyridine, DMSO, 0°C, 2 h; c) *t*BuOK, Ph_3PCHBr_2·Br, THF, RT, 12 h, 78% over 2 steps; d) Me_3SiBr, CH_2Cl_2, 0°C, 30 min, >98% (SEM = trimethylsilylethoxymethyl.

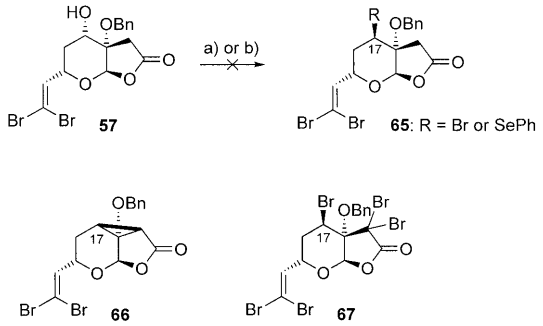
Initially, we targeted **58** as our coupling partner and accordingly the secondary alcohol in **57** was converted to the corresponding xanthate **64** (Scheme 14). Although this reaction occurred in excellent yield, the xanthate functionality could not be carried through subsequent steps owing to its propensity to undergo a rapid elimination reaction.

Efforts were then directed towards the installation of a selenide or a bromide at the C17 position to provide access



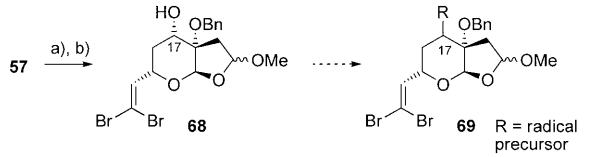
Scheme 14. Options for introducing a radical precursor at C17: xanthate formation. a) CS_2, $NaN(SiMe_3)_2$, THF, −78°C, 30 min *then* MeI, −78°C, 1 h, 85%.

to propargylic mesylates **59** and **60** in the hope that these would prove more stable than the aforementioned axial xanthate **64**. Unfortunately, conditions could not be found to effect conversion of **57** to the radical precursor **65**. Instead, alternative pathways were observed in which the adjacent lactone displayed competitive reactivity leading to cyclopropane **66** and pentabromo derivative **67** (Scheme 15).



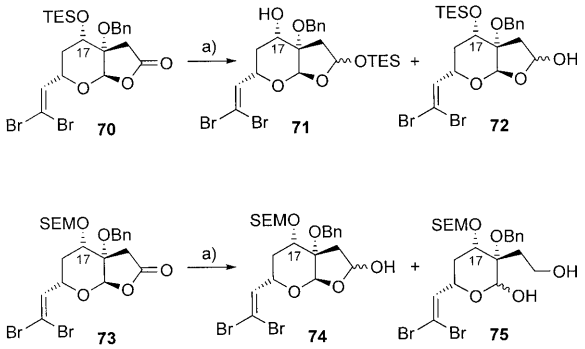
Scheme 15. Options for introducing a radical precursor at C17: bromide and selenide formation. a) CBr_4, PPh_3 CH_2Cl_2, 24 h, **66** (32%), **67** (31%); b) PhSe-phthalimide, CH_2Cl_2, 2 h, **66** (51%).

In view of this result, we opted to install the requisite methyl acetal unit prior to functionalisation at C17. Lactone **57** was therefore subjected to a reduction/methanolysis sequence but this procedure proved unsatisfactory: whilst diisobutylaluminium hydride (DIBAL-H) cleanly effected reduction of **57** to the corresponding lactol, the requisite methyl acetal **68** could never be accessed in acceptable yield owing to competing side reactions (Scheme 16).



Scheme 16. Options for introducing a radical precursor at C17: a) DIBAL-H, CH_2Cl_2, −78°C, 3.5 h; b) MeOH, Amberlyst-15, 3 Å sieves, MeCN, RT, 24 h, 57% over 2 steps (with accompanying aldehyde by-products).

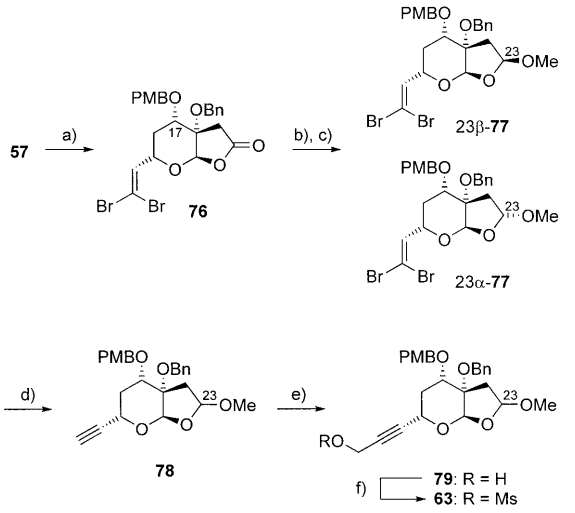
Based on earlier findings, we settled on an approach in which the C17 MOM ether would be directly exchanged for an alternative protecting group. It was anticipated that this protecting group could then be transformed to the desired radical precursor at a later stage in the synthesis. Although intermediate **57** could be cleanly converted to the corresponding triethylsilyl (TES) ether **70**, the ensuing lactone reduction then led to about 50% migration of the silyl ether group to give **71**, a problem which proved insurmountable (Scheme 17). A trimethylsilylethoxymethyl (SEM) ether was therefore employed to overcome this migration problem. Disappointingly, although the corresponding SEM ether **73** could be prepared in quantitative yield, lactone reduction



Scheme 17. Options for introducing a protecting group at C17. a) DIBAL-H, CH_2Cl_2, −78 °C, 30 min.

then proved non-selective and upon treatment of **73** with 1.0 equiv of DIBAL-H a 1:1:1 mixture of starting material **73**, lactol **74** and diol **75** was observed which could not be optimised in favour of **74**.

While the above studies were tedious and frustrating, we reasoned that the use of a *para*-methoxybenzyl (PMB) ether could solve our problems. Finally, after exhaustive studies, we were eventually able to prepare **76** in excellent yield employing PMB trichloroacetimidate and lanthanum triflate as catalyst (Scheme 18).[78] Reduction/methanolysis of **76** then proceeded smoothly to afford methyl acetals 23α-**77** and 23β-**77** as a 1:1.5 mixture, which were readily separated by column chromatography. Both epimers were deemed viable precursors for azadirachtin (**1**) but were carried forward individually to provide propargylic mesylates 23α-**63** and 23β-**63** in good overall yield.[79]



Scheme 18. Introduction of the C17 PMB ether and subsequent manipulation to form the propargylic mesylate **63**. a) PMB-TCA, $La(OTf)_3$, PhMe, RT, 3 h, 90%; b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; c) MeOH, Amberlyst-15, MeCN, RT, 12 h, 49% 23α-**77**, 25% 23β-**77** over 2 steps; d) MeLi·LiBr, THF, −78 °C, 2 h, 97% with 23α-**77**, 93% with 23β-**77**; e) *i*PrMgCl, THF, 45 °C, 30 min, *then* $(CH_2O)_n$, 45 °C, 1.5 h, 89% with 23α-**78**, 5 h, 78% with 23β-**78**; f) Ms_2O, iPr_2NEt, CH_2Cl_2, 0 °C, 30 min, 90% with 23α-**79**, 90% with 23β-**79** (TCA = 1,1,1-trichloroacetimidate).

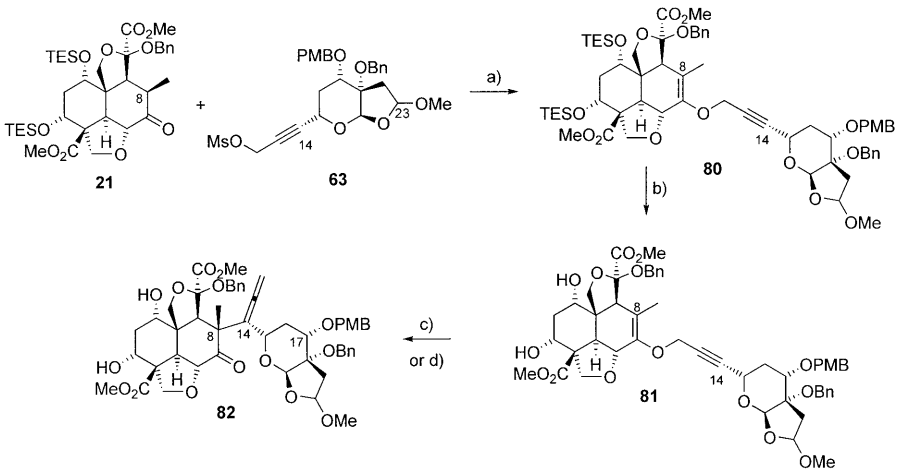
Fragment coupling and construction of the [3.2.1] bicycle: With a reliable and scalable route to the new propargylic mesylate coupling partners (23α-**63** and 23β-**63**) established, we were in a position to examine the key fragment union (Scheme 19). Preliminary work employed the reaction conditions developed earlier,[67] namely a 5:1 ratio of mesylate **63** to decalin ketone **21** with 8.0 equiv of sodium hydride and 5.0 equiv of [15]crown-5. However, this resulted in extensive decomposition of both decalin **21** and propargylic mesylate **63**, which was presumably due to the excess of sodium hydride employed in this step. Frustrated by this loss of the precious mesylate **63**, we decided to test whether an excess of decalin ketone **21** could be employed for the coupling process, as this material was readily available through degradation.[54] The quantity of sodium hydride present in this reaction was also reduced and ultimately, the preparation of the propargylic enol ethers 23α-**80** and 23β-**80** was achieved from the corresponding mesylates in excellent yield. The optimal conditions utilised a 5:1 ratio of decalin ketone **21** to propargylic mesylate **63** in conjunction with 4.9 equiv of sodium hydride. Fortunately, any unreacted decalin (**21**) could be recovered by column chromatography and re-used in further coupling reactions.

We next investigated the critical C8−C14 bond formation by Claisen rearrangement of propargylic enol ether **80**, but again this proved difficult. Previous work[67] had suggested that the axial triethylsilyl ether groups present in **80** create a sterically congested environment, which inhibits the Claisen process. Accordingly, diol **81** was prepared and we were pleased to find that this could be converted to our target allene **82** either by microwave irradiation or by gold(I) catalysis.[80]

Efforts were then focussed on the manipulation of the C17 PMB ether in **82** to provide an appropriate radical precursor in preparation for the next key carbon−carbon bond forming event. It was therefore necessary to reprotect the 1,3-diol unit present in **82**, prior to cleavage of the PMB ether. Disappointingly, conditions could not be found to effect formation of the C1,C3-bis-acetate (Table 1, entries 1–3). It appeared that the C3 hydroxyl group was substantially more reactive than its C1 neighbour, and whilst mild conditions effected selective protection at C3, forcing conditions resulted in a complex mixture, derived from poly-aldol condensation at the C1/C3 acetate groups (Table 1, entry 4).

Although the use of a trifluoroacetate protecting group circumvented this problem (Table 1, entry 5), the resulting compound was found to be extremely labile and decomposed upon standing. The introduction of a benzylidene acetal, commonly used for the protection of 1,3-diols, also met with failure (Table 1, entry 6). Eventually, we decided to install a silyl ether at C3 (Table 1, entry 7) in the hope that the poor reactivity of the C1 hydroxyl group would negate the need for its protection.

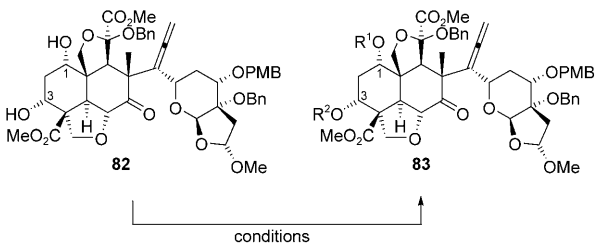
Pleasingly **82** was converted to triethylsilyl ether **84** in quantitative yield and the C17 PMB ether was then readily cleaved under standard conditions (Scheme 20). The next task was to install a radical precursor at C17 and for this,



Scheme 19. Fragment union and installation of the C8-C14 bond by Claisen rearrangement. a) NaH, [15]crown-5, THF, −78 °C, 3 h, 82 % with 23α-**63**, 74 % with 23β-**63**; b) TBAF, THF, 0 °C , 10 min, 90 % with 23α-**80**, >98 % with 23β-**80**; c) DCB, microwave irradiation, 180 °C, 4×5 min, 86 % with 23α-**81**, 83 % with 23β-**81** or 72 % over 3 steps when used crude; d) $(Ph_3PAu)_3O{\cdot}BF_4$, CH_2Cl_2, RT, 24 h, 81 % with 23α-**81**.

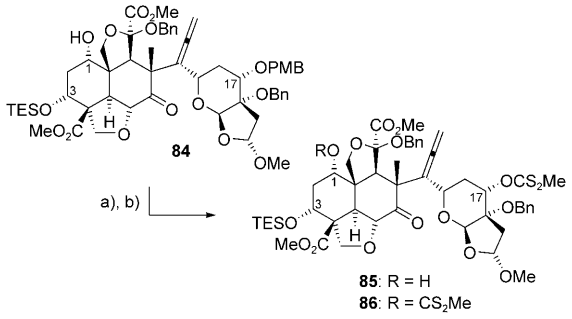
the xanthate group was again selected as this had been used successfully in previous studies.[67] Under optimised conditions significant quantities of bis-xanthate **86** were observed in addition to the desired product **85** and we therefore chose to re-evaluate our C1/C3 protecting group strategy. We reasoned that the installation of a larger silyl ether at C3 would retard this undesired bis-xanthate formation and consequently, diol **82** was converted to the corresponding C3 TBS ether (Scheme 21). Cleavage of the C17 PMB ether and xanthate formation under optimised conditions led to good isolated yields of the desired product **87**.

Table 1. Protection of the C1/C3 diol.

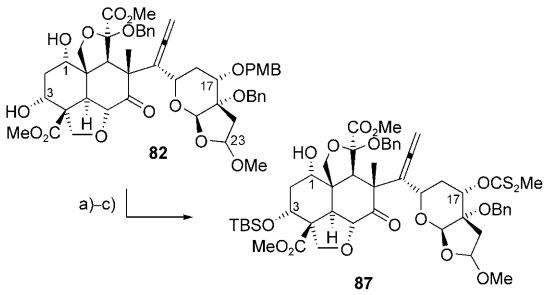


Entry	Conditions	Result
1	isopropenyl acetate, PPTS, RT	no reaction
2	Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT	R^1=H, R^2=Ac
3	Ac_2O, NEt_3, DMAP, CH_2Cl_2, reflux	R^1=H, R^2=Ac
4	Ac_2O, pyridine, DMAP, 40 °C	R^1, R^2=aldol product[a]
5	$(CF_3CO)_2O$, pyridine, DMAP, 40 °C	R^1, R^2=$COCF_3$
6	$PhCH(OMe)_2$, PPTS, 4 Å sieves, RT, CH_2Cl_2	decomposition
7	TESOTf, *i*Pr_2NEt, CH_2Cl_2, −78 °C	R^1=H, R^3=TES

[a] Under the forcing reaction conditions the bis-acetyl product underwent an aldol condensation with Ac_2O to give a complex mixture of C1/C3 esters.



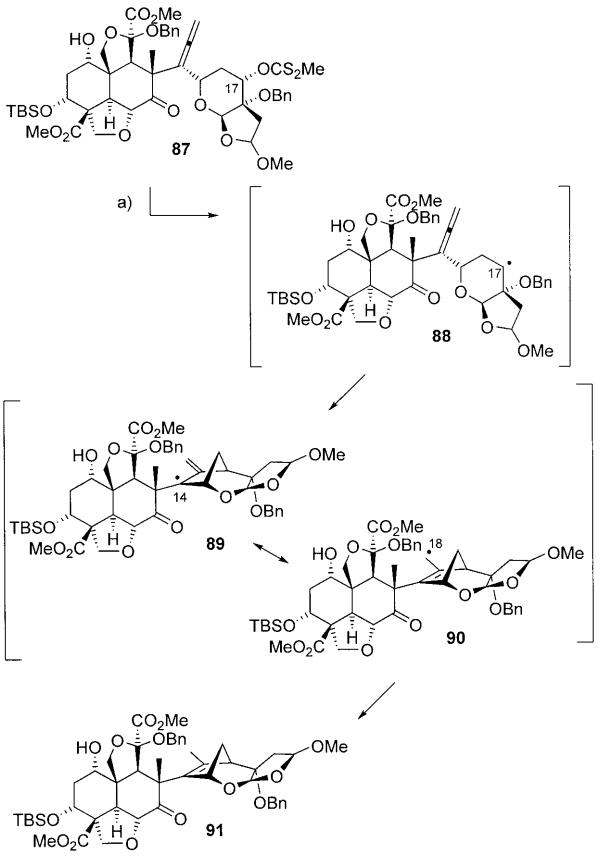
Scheme 20. Xanthate formation in the presence of a C3 TES ether. a) DDQ, CH_2Cl_2, H_2O, 0 °C, 2 h, 87 %; b) CS_2, $NaN(SiMe_3)_2$, THF, −78 °C, 30 min *then* MeI, −78 °C, 30 min, 61 %.



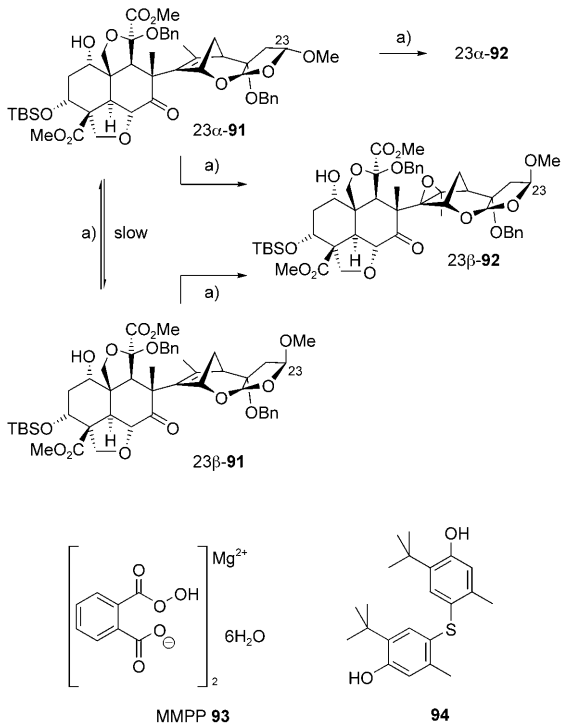
Scheme 21. Xanthate formation in the presence of a C3 TBS ether. a) TBS-imidazole, DMF, 80 °C, 2 h, 91 % with 23α-**82**, 86 % with 23β-**82**; b) DDQ, pH 7 buffer, CH_2Cl_2, H_2O, RT, 3 h, 91 % for 23α, 95 % for 23β; c) CS_2, $NaN(SiMe_3)_2$, THF, −78 °C, 30 min, then MeI, −78 °C, 1 h, 86 % for 23α, 57 %, 81 % brsm for 23β.

Finally, with radical precursor **87** in hand, the stage was set for the crucial carbon–carbon bond forming event (Scheme 22). Tributyltin hydride and AIBN were added to a dilute solution of xanthate **87** and AIBN at 110 °C over 2 h and the resulting mixture heated for a further 12 h. Upon analysis of the crude reaction, we were delighted to find that the desired radical cyclisation had taken place to give the [3.2.1] bicycle **91** with exquisite selectivity. We rationalised that the efficiency of the 5-*exo* cyclisation was due to the reactive conformation of **88** in which the central allene carbon is extremely close in space to the C17 centred radical. Whilst quenching of the C14 tertiary radical in **89** would yield the undesired *exo* alkene, this centre is highly congested, and thus the desired *endo* alkene **91** is formed through quenching of the less hindered C18 primary radical in **90**.

Installation of the tetrasubstituted epoxide: Although we had overcome a considerable hurdle in the synthesis of



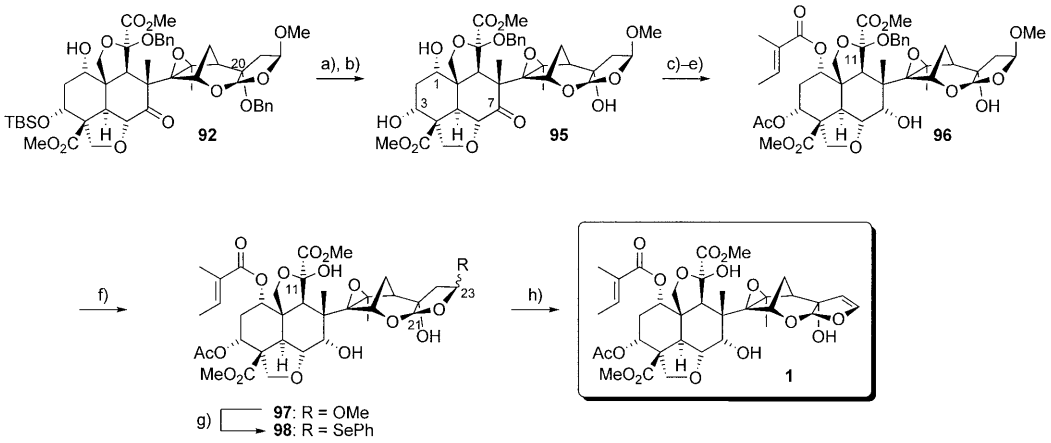
Scheme 22. Proposed mechanism for the 5-*exo* radical cyclisation. a) Bu_3SnH, AIBN, PhMe, 110 °C, 12 h, 90 % with 23α-**87**, 91 % with 23β-**87**.



Scheme 23. MMPP-mediated epoxidation of the hindered olefin **91**. a) **93**, **94**, $NaHCO_3$, MeOH, 110 °C, sealed tube, 7 d, 22 %, 89 % brsm with 23α-**92**, 65 %, 95 % brsm, with 23β-**92**.

[3.2.1] bicycle **91**, we were immediately presented with another challenging transformation, namely epoxidation of the hindered tetrasubstituted olefin. Typically the use of *meta*-chloroperbenzoic acid (*m*CPBA) has been reported to bring about such a transformation either at ambient or at elevated temperatures.[81] However, **91** failed to react with *m*CPBA even upon reflux in CH_2Cl_2 for an extended period of time. In fact, many typical oxidation procedures were screened without success. Even very vigorous oxidants such as dimethyl or methyltrifluoromethyl dioxirane failed to perform the required epoxidation but led instead to oxidative debenzylation or decomposition. Nevertheless, our persistence was finally rewarded when we found that the commercially available magnesium monoperoxyphthalate hexahydrate (MMPP)[82] **93** could achieve this mischievous transformation (Scheme 23). However, the reaction was only successful in methanol at elevated temperatures (110 °C, sealed tube) using the radical inhibitor **94** to extend the longevity of the peracid to seven days! Whilst all preliminary studies were performed on the C23 alkene 23α-**91**, thorough analysis of the product ^1H NMR spectrum and comparison with an authentic sample[83] revealed that the β-epoxide **92** had in fact been formed. Treatment of β-alkene 23β-**91** under identical conditions also resulted in the formation of β-epoxide **92**, but in this case a higher yield was observed. We rationalise this observation by assuming that only the β-alkene 23β-**91** is reactive to epoxidation, and that under the reaction conditions the α-alkene 23α-**91** can undergo gradual epimerisation prior to oxidation. This hypothesis is supported both by the presence of a mass ion corresponding to an intermediate C23 lactol and the observed stability of the α-epoxide 23α-**93**[83] to the MMPP epoxidation conditions.

Final steps: At this stage we had substantial quantities of material with which to complete the synthesis, both from the synthesis described thus far and from degradation of the natural product.[83] Desilylation of **92** with TBAF was followed by selective cleavage of the C20 benzyl ether after 3 h to generate **95** in excellent yield (Scheme 24). Selective acetylation at the C3 position of **95** was then achieved under standard conditions to provide the C3 acetate. Although esterification of the hindered C1 hydroxyl group proved problematic, we were ultimately able to effect this transformation with a tiglic acid/Yamaguchi mixed anhydride developed previously within our group.[84] Reduction of the C7 carbonyl group proceeded chemoselectively under Luche[85] conditions, but stereocontrol in this process could not be achieved.[86] As a result, a 1:1 diastereomeric mixture was obtained, from which the unwanted equatorial alcohol could be reoxidised and subsequently recycled providing **96** in yields of up to 75 % after one iteration. Cleavage of the remaining benzyl ether in **96** then proceeded without incident to furnish an intermediate C11 lactol (**97**) in good yield, with no concomitant reduction of the tiglate functionality. Finally, it was time to unmask the labile enol ether function-



Scheme 24. Final steps leading to the completion of the first synthesis of azadirachtin **1**. a) TBAF, THF, 0 °C, 1 h, 95 %; b) H_2 , Pd/C, EtOH, RT, 3 h, 95 %; c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, 4 h, 76 %; d) $MeCHCMeCO_2COC_6H_2Cl_3$, Cs_2CO_3, PhMe, reflux, 6 d, 50 % (95 % brsm); e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 4 h, 49 %; f) H_2, Pd/C, MeOH, RT, 14 h, 81 %; g) PhSeH, PPTS, $C_2H_4Cl_2$, reflux, 4 h; h) H_2O_2, pyridine, 0 °C, 5 min, 85 % over 2 steps.

ality present in the natural product. This would first require selective manipulation of the C23 methyl acetal in **97** in the presence of acetals at C11 and C21, itself a challenging task. Furthermore, our choice of reagents was severely limited owing to the instability of azadirachtin and its derivatives under acidic and basic conditions. Nonetheless, following extensive experimentation, we found that methyl acetal **97** could be cleanly converted to the epimeric selenoacetals **98** using benzene selenol and pyridinium *para*-toluenesulfonate (PPTS).[87] Upon oxidation of **98**, spontaneous elimination of phenylselenenic acid then occurred to provide azadirachtin **1**, which was found to be identical in all respects to the natural material![87]

Conclusion

While herein we report the successful outcome of the synthesis of azadirachtin, we also wish to share with readers some of the problems and frustrations that were encountered along the way. Synthesis is not always straight-forward and both effort and commitment are often required to surmount the barriers and recover from the dead-ends. All of these trials and tribulations teach us many things, not least of which is how to learn from these failed experiments. Importantly, throughout this synthesis programme, we have gained access to materials that can aid our understanding of the biological profile of this fascinating molecule. However, we hope that it is the new chemistry developed in this synthesis that will have a lasting influence. The advances of which we are most proud include the use of a silicon substituent to control intramolecular Diels–Alder reactions as well as stereoselective events in the formation of the decalin portion of azadirachtin. The oxidative ring contraction designed to install the hemiacetal feature in the natural product also represents a neat solution to a potentially difficult functional group combination.

Perhaps the most impressive aspect of the synthesis is the coupling of highly functionalised fragments through *O*-alkylation and subsequent propargylic Claisen rearrangement to establish the very hindered C8–C14 bond in azadirachtin. In fact, we believe this to be one of the most functionally complex examples of this process to have ever been reported. Moreover, the ensuing radical cyclisation onto the newly formed allene sets up the entire carbon skeleton of the right hand portion of the natural product in a single operation. Finally, the last steps of the synthesis clearly demonstrate the need for careful planning, particularly when faced with a diverse array of highly sensitive functionalities such as those found in azadirachtin.

per ardua ad alta!

Experimental Section

General information: Where appropriate, reactions were performed using oven-dried glassware under an argon atmosphere. Solvents were distilled before use, petrol = petroleum ether (40–60 °C). Melting points were determined using Reichert Hot-Stage apparatus, equipped with a digital thermometer. Optical rotation was measured using a Perkin–Elmer Polarimeter 343 with the sample temperature maintained at 25 °C unless otherwise stated ($c = 1.0$ implies 10 mg mL^{-1}). ^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz), a Bruker Avance (500 MHz) fitted with dual cryoprobe or a Bruker DRX 600 (600 MHz) spectrometer using the deuterated solvent as internal deuterium lock. Chemical shift data are given relative to residual protic solvent where $\delta(CHCl_3) = 7.26$ ppm. ^{13}C NMR spectra were recorded on a Bruker DPX-400 (100 MHz), a Bruker Avance (125 MHz) or a Bruker DRX 600 (150 MHz) spectrometer with broadband proton decoupling using the deuterated solvent as internal deuterium lock. Chemical shift data are given relative to the solvent, where $\delta(CDCl_3) = 77.0$ ppm, t. NMR spectra were assigned using information ascertained from DEPT, COSY, HMBC, HMQC and NOE experiments. These assignments were made according to the natural product numbering of azadirachtin (Figure 3) and compounds were named according to IUPAC guidelines. IR spectra were recorded on a Perkin–Elmer Spectrum I FTIR spectrometer. High resolu-

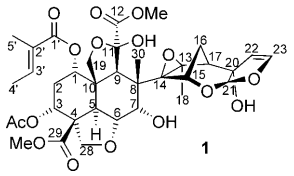


Figure 3. Numbering of azadirachtin **1**.

tion mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier or an Applied Biosystems PE SCIEX QSTAR spectrometer. Flash column chromatography was carried out using silica gel [Merck 9385].

Numbered compounds which are suffixed with **a**, **b** or **c** refer to intermediates obtained from manipulation of the appropriate compounds, which have been omitted from certain schemes for reasons of clarity. Each intermediate is isolated after one (a), two (b) or three (c) transformations from the numbered compound.

4,6-*O*-Benzylidene-(pent-4-enyl)-β-D-galactopyranoside (39): Diol **39** was prepared according to the literature procedure.[69] M.p. 148–149 °C (lit. 158–160 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 2H; Ph), 7.39–7.34 (m, 3H; Ph), 5.83 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H; pentenyl H4), 5.56 (s, 1H; OC*H*PhO), 5.05 (dd, J = 17.0, 1.6 Hz, 1H; pentenyl H5$_Z$), 4.98 (dd, J = 10.2, 1.6 Hz, 1H; pentenyl H5$_E$), 4.33 (dd, J = 12.5, 1.2 Hz, 1H; H14), 4.27 (d, J = 7.5 Hz, 1H; H21), 4.20 (m, 1H; H16), 4.09 (dd, J = 12.5, 1.8 Hz, 1H; H14), 3.99 (dt, J = 9.4, 6.6 Hz, 1H; pentenyl H1), 3.76 (ddd, J = 9.3, 7.5, 1.6 Hz, 1H; H20), 3.72 (ddd, J = 9.3, 8.8, 3.7 Hz, 1H; H17), 3.53 (dt, J = 9.4, 6.9 Hz, 1H; pentenyl H1), 3.48 (m, 1H; H15), 2.47 (d, J = 8.8 Hz, 1H; OH), 2.43 (d, J = 1.6 Hz, 1H; 20OH), 2.16 (dt, J = 7.2 Hz, 6.8 Hz, 2H; 2×pentenyl H3), 1.82–1.70 ppm (m, 2H; 2×pentenyl H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1 (d), 137.4 (s), 129.2 (d), 128.2 (2×d), 126.3 (2×d), 114.9 (t), 102.7 (d), 101.4 (d), 75.2 (d), 72.6 (d), 71.8 (d), 69.3 (t), 69.1 (t), 66.6 (d), 30.1 (t), 28.6 ppm (t); IR (film): ν_{max} = 3480, 2910, 1720, 1450, 1400, 1370, 1270, 1170, 1070, 1030, 910 cm^{-1}; HRMS: m/z: calcd for $C_{18}H_{24}NaO_6$: 359.1471; found: 359.1479 [M+Na]$^+$, Δ = 2.2 ppm. Recorded data consistent with literature values.[69]

4,6-*O*-Benzylidene-3-*O*-methoxymethyl-(pent-4-enyl)-β-D-galactopyranoside (41): Di-*n*-butyltin oxide (26.7 g, 107 mmol) was added to a stirred solution of diol **39** (34.4 g, 102 mmol) in MeOH (340 mL). The reaction mixture was heated under reflux for 2 h during which time it became transparent. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo. To ensure complete removal of MeOH, the crude product was re-dissolved in toluene and concentrated in vacuo to yield the crude stanylidene acetal **40**. Chloromethyl methyl ether (8.23 mL, 108 mmol) was added dropwise to a stirred solution of the crude stanylidene acetal **40** (ca. 102 mmol) in 1,4-dioxane (200 mL). The reaction mixture was stirred at 55 °C for 1.5 h and then the reaction was quenched by the addition of water (100 mL). The mixture was extracted with ethyl acetate (3×200 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (10–50 % ethyl acetate in petrol) to yield alcohol **41** (36.1 g, 93 %) as a white solid. M.p. 49–51 °C; $[\alpha]_D$ = −4.5 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (m, 2H; Ph), 7.37–7.31 (m, 3H; Ph), 5.83 (ddt, J = 17.0, 10.0, 6.6 Hz, 1H; pentenyl H4), 5.54 (s, 1H; OC*H*PhO), 5.04 (dd, J = 17.0, 1.5 Hz, 1H; pentenyl H5$_Z$), 4.98 (dd, J = 10.0, 1.5 Hz, 1H; pentenyl H5$_E$), 4.86 (d, J = 7.0 Hz, 1H; OC*H*HO), 4.82 (d, J = 7.0 Hz, 1H; OCH*H*O), 4.35–4.28 (m, 3H; H21, H16, H14), 4.07 (dd, J = 12.4, 1.7 Hz, 1H; H14), 3.99 (dt, J = 9.5, 6.7 Hz, 1H; pentenyl H1), 3.95 (ddd, J = 9.6, 8.0, 1.7 Hz, 1H; H20), 3.62 (dd, J = 9.6, 3.6 Hz, 1H; H17), 3.55 (dt, J = 9.5, 7.0 Hz, 1H; pentenyl H1), 3.45–3.42 (m, 1H; H15), 3.43 (s, 3H; OMe), 2.67 (d, J = 1.7 Hz, 1H; OH), 2.16 (dd, J = 14.1, 7.2 Hz, 2H; 2×pentenyl H3), 1.83–1.73 ppm (m, 2H; 2×pentenyl H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (s), 137.8 (d), 129.0 (d), 128.1 (2×d), 126.4 (2×d), 114.8 (t), 103.1 (d), 101.3 (d), 96.9 (t), 79.1 (d), 74.9 (d), 69.6 (d), 69.2 (t), 69.2 (t), 66.6 (d), 55.8 (q), 30.2 (t), 28.7 (t); IR (film): ν_{max} = 3460, 2900, 1450, 1400, 1370, 1170, 1150, 1110, 1090, 1040, 1000, 920 cm^{-1}; HRMS: m/z: calcd for 403.1737 [(M+Na)$^+$ $C_{20}H_{28}NaO_7$ requires 403.1733] Δ = 1.1 ppm.

2-Allyl-4,6-*O*-benzylidene-3-*O*-methoxymethyl-(pent-4-enyl)-β-D-talopyranoside (42): *i*Pr_2NEt (3.6 mL, 21.05 mmol) was added to a stirred solution of secondary alcohol **41** (2.0 g, 5.26 mmol) in CH_2Cl_2 (150 mL) at room temperature. The mixture was cooled to 0 °C and then a solution of SO_3·pyridine (2.51 g, 15.8 mmol) in dimethylsulfoxide (10 mL) was added drop wise. The reaction mixture was stirred at 0 °C for 30 min and then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and allowed to reach room temperature. The mixture was extracted with CH_2Cl_2 (2×100 mL) and the organic layers combined, washed with saturated aqueous $CuSO_4$ solution (2×100 mL), dried ($MgSO_4$) and concentrated in vacuo. Allyl magnesium chloride (2.0 M solution in THF, 5.26 mL, 10.52 mmol) was added to a stirred solution of the crude ketone in THF (100 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (75 mL). The mixture was extracted with ethyl acetate (2×100 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The mixture was extracted with ethyl acetate (3×50 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (10–100 % ethyl acetate in petrol) to yield homoallylic alcohol **42** (21.0 g, 85 % over 2 steps) as a white solid. M.p. 79–81 °C; $[\alpha]_D$ = −18.8 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2H; Ph), 7.34–7.30 (m, 3H; Ph), 5.88–5.70 (m, 2H; pentenyl H4, H23), 5.50 (s, 1H; OC*H*PhO), 5.17 (dd, J = 17.2, 2.0 Hz, 1H; 23 = CH$_Z$), 5.13 (dd, J = 10.4, 2.0 Hz, 1H; 23 = CH$_E$), 5.04 (dd, J = 17.1, 1.6 Hz, 1H; pentenyl H5$_Z$), 4.97 (dd, J = 10.4, 1.6 Hz, 1H; pentenyl H5$_E$), 4.90 (d, J = 7.2 Hz, 1H; OC*H*HO), 4.78 (d, J = 7.2 Hz, 1H; OCH*H*O), 4.44 (br d, J = 3.2 Hz, 1H; H16), 4.40 (dd, J = 12.4, 1.3 Hz, 1H; H14), 4.26 (d, J = 12.4, 1.2 Hz, 1H; H21), 4.08 (dd, J = 12.4, 1.6 Hz, 1H; H14), 4.01 (dt, J = 9.4, 6.4 Hz, 1H; pentenyl H1), 3.77 (s, 1H; OH), 3.55 (d, J = 3.2 Hz, 1H; H17), 3.51–3.46 (m, 1H; pentenyl H1), 3.46 (s, 3H; OMe), 3.36 (m, 1H; H15), 2.66 (dd, J = 13.6, 7.8 Hz, 1H; H22), 2.56 (dd, J = 13.6, 7.6 Hz, 1H; H22), 2.25–2.09 (m, 2H; 2×pentenyl H3), 1.88–1.68 ppm (m, 2H; 2×pentenyl H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (d), 137.2 (s), 132.8 (d), 129.1 (d), 128.2 (2×d), 126.1 (2×d), 119.1 (t), 114.8 (t), 102.2 (d), 101.5 (d), 96.7 (t), 77.2 (s), 75.6 (d), 74.1 (d), 69.4 (t), 69.3 (t), 66.6 (d), 56.1 (q), 36.4 (t), 30.2 (t), 28.7 ppm (t); IR (film): ν_{max} = 3510, 2920, 2860, 1640, 1450, 1400, 1370, 1330, 1250, 1220, 1170, 1150, 1120, 1050, 1020, 990, 910, 750 cm^{-1}; HRMS: m/z: calcd for $C_{23}H_{32}NaO_7$: 443.2046; found: 443.2045 [M+Na$^+$], Δ = 0.2 ppm.

2-Allyl-2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methoxymethyl-(pent-4-enyl)-β-D-talopyranoside (43): Sodium hydride (60 % dispersion in mineral oil, 5.33 g, 133 mmol) was added to a stirred solution of homoallylic alcohol **42** (28.0 g, 66.6 mmol) in DMF (200 mL) at 0 °C. The reaction mixture was stirred for 45 min before benzyl bromide (15.8 mL, 133 mmol) was added and the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred for 18 h before the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (150 mL). The mixture was extracted with diethyl ether (3×300 mL) and the organic layers were combined, washed with aqueous LiCl solution (10 % wt/vol) (3×500 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (10–50 % ethyl acetate in petrol) to yield benzyl ether **43** (31.4 g, 92 %) as a white solid. M.p. 63–65 °C; $[\alpha]_D$ = −8.9 (c = 0.93 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.4 Hz, 2H; Ph), 7.36–7.08 (m, 8H; Ph), 5.91–5.79 (m, 2H; H23, pentenyl H4), 5.50 (s, 1H; OC*H*PhO), 5.19 (dd, J = 17.1, 1.5 Hz, 1H; 23 = CH$_Z$), 5.14 (dd, J = 10.1, 1.5 Hz, 1H; 23 = CH$_E$), 5.08 (d, J = 12.2 Hz, 1H; C*H*HPh), 5.03 (ddd, J = 17.3, 3.2, 1.6 Hz, 1H; pentenyl H5$_Z$), 4.97 (br d, J = 10.2 Hz, 1H; pentenyl H5$_E$), 4.91 (d, J = 7.1 Hz, 1H; OC*H*HO), 4.87 (d, J = 12.2 Hz, 1H; CH*H*Ph), 4.76 (d, J = 7.1 Hz, 1H; OCH*H*O), 4.43 (d, J = 12.5 Hz, 1H; H14), 4.34 (dd, J = 3.8, 1.0 Hz, 1H; H16), 4.33 (s, 1H; H21), 4.11 (dd, J = 12.5, 2.1 Hz, 1H; H14), 4.01 (dt, J = 9.1, 6.3 Hz, 1H; pentenyl H1), 3.65 (d, J = 3.8 Hz, 1H; H17), 3.46 (s, 3H; OMe), 3.41 (dt, J = 9.1, 6.8 Hz, 1H; pentenyl H1), 3.32 (m, 1H; H15), 2.85 (dd, J = 13.3, 7.5 Hz, 1H; H22), 2.79 (dd, J = 13.3, 7.6 Hz, 1H; H22), 2.21–2.10 (m, 2H; 2×pentenyl H3), 1.81–1.68 ppm (m, 2H; 2×pentenyl

H2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 140.7 (s), 138.2 (d), 138.0 (s), 133.6 (d), 128.5 (d), 127.9 (2×d), 127.6 (2×d), 127.1 (2×d), 126.6 (2×d), 126.1 (d), 118.8 (t), 114.7 (t), 103.6 (d), 101.4 (d), 96.4 (t), 77.5 (d), 76.9 (s), 73.3 (d), 69.5 (t), 69.4 (t), 67.3 (d), 66.6 (t), 56.0 (q), 34.9 (t), 30.3 (t), 28.9 ppm (t); IR (film): ν_{max} = 3070, 3030, 2920, 2880, 1640, 1500, 1450, 1370, 1170, 1150, 1110, 1090, 1040, 1030, 990, 910 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{30}H_{38}NaO_7$: 533.2515; found: 533.2512 [*M*+Na$^+$], Δ = 0.6 ppm.

(2*S*,4a*R*,5a*R*,7*R*,8a*S*,9*S*,9a*S*)-8a-Benzyloxy-7-bromomethyl-9-methoxymethoxy-2-phenyloctahydrofuro[3′,2′:5,6]pyrano[3,2-*d*,1,3]dioxin (44) and 2-allyl-2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-methoxymethyl-D-talose (45): A solution of freshly recrystallised *N*-bromosuccinimide (3.67 g, 20.6 mmol) in acetonitrile (50 mL) was added dropwise to a stirred solution of pent-4-enyl pyranoside **43** (5 g, 9.8 mmol) in acetonitrile (100 mL) and aqueous pH 7 buffer solution (7.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and then the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (100 mL). The mixture was extracted with diethyl ether (3×100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (15% ethyl acetate in petrol) to afford a 1.4:1 mixture of bromoalkane **44** and lactol **45** (2.69 g, 58%) as a pale yellow oil. Data for **44**: $[\alpha]_D$ = +42.9 (*c* = 0.35 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.3 Hz, 2H; Ph), 7.34–7.30 (m, 3H; Ph), 7.26 (dd, *J* = 7.4, 7.4 Hz, 2H; Ph), 7.24–7.21 (m, 3H; Ph), 5.69 (s, 1H; H21), 5.56 (s, 1H; OC*H*PhO), 5.07 (d, *J* = 11.6 Hz, 1H; C*H*HPh), 4.92 (d, *J* = 7.1 Hz, 1H; OC*H*HO), 4.81 (d, *J* = 7.1 Hz, 1H; OCH*H*O), 4.75 (d, *J* = 11.6 Hz, 1H; CH*H*Ph), 4.41 (m, 1H; H23), 4.35 (d, *J* = 2.8 Hz, 1H; H16), 4.32 (d, *J* = 12.6 Hz, 1H; H14), 4.08 (dd, *J* = 12.6, 1.1 Hz, 1H; H14), 3.84 (br, 1H; H15), 3.83 (d, *J* = 2.8 Hz, 1H; H17), 3.55–3.49 (m, 2H; CH_2Br), 3.48 (s, 3H; OMe), 2.68 (dd, *J* = 12.7, 6.9 Hz, 1H; H22), 2.13 ppm (dd, *J* = 12.7, 8.8 Hz, 1H; H22); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.1 (s), 137.7 (s), 128.6 (d), 127.9 (2×d), 127.8 (2×d), 127.1 (2×d), 126.8 (d), 126.4 (2×d), 104.0 (d), 101.1 (d), 95.8 (t), 77.6 (s), 76.4 (d), 74.4 (d), 71.5 (d), 69.7 (t), 69.2 (t), 64.1 (d), 55.8 (q), 37.6 (t), 36.2 ppm (t); IR (film): ν_{max} = 2920, 1720, 1450, 1370, 1310, 1250, 1160, 1100, 1020, 980, 920 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{25}H_{29}BrNaO_7$: 543.0994; found: 543.0979 [*M*+Na$^+$], Δ = 2.8 ppm.

(2*S*,4a*R*,5a*R*,8a*S*,9*S*,9a*S*)-8a-Benzyloxy-9-methoxymethoxy-2-phenyl-octahydrofuro[3′,2′:5,6]pyrano[3,2-*d*,1,3]dioxin-7-one (47): NH_4Cl (3.39 g, 63.3 mmol) followed by activated zinc dust (8.28 g, 127 mmol) was added to a stirred solution of bromoalkane **44** (6.6 g, 12.7 mmol) in ethanol (dry, 333 mL). The reaction mixture was heated under reflux for 2 h then allowed to cool to room temperature. Diethyl ether (350 mL) was added and the solids were removed by filtration through Celite. The filtrate was concentrated in vacuo to give hemiacetal **45** as a crude mixture of C21 anomers (5:1 by ^{1}H NMR). Ozone was bubbled through a stirred solution of crude δ-lactol **45** (ca. 12.7 mmol) in CH_2Cl_2 (600 mL) at −78 °C for 15 min during which time the solution turned a pale blue. Oxygen was then bubbled through the reaction mixture for 15 min at −78 °C to remove excess dissolved ozone, during which time the blue colour faded. Polystyrene supported triphenyl phosphine (3 mmol g^{-1}, 12.7 g, 38.0 mmol) was added and the reaction mixture allowed to reach room temperature over 18 h. The polymer supported reagents were removed by filtration and the filtrate was concentrated in vacuo to yield crude γ-lactol **46** as a white foam. 4 Å molecular sieves (6.0 g) were added to a stirred solution of crude γ-lactol **46** (ca. 12.7 mmol) in acetonitrile (400 mL). The mixture was stirred at room temperature for 15 min then was cooled to 0 °C and *N*-methylmorpholine-*N*-oxide (2.22 g, 19.0 mmol) followed by tetra-*n*-propyl ammonium perruthenate (445 mg, 1.3 mmol) was added. The reaction mixture was stirred at room temperature for 1 h before the mixture was concentrated in vacuo. Filtration through silica gel (eluting with 33% CH_2Cl_2 in diethyl ether) afforded γ-lactone **47** (4.24 g, 76% over 3 steps) as a white foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.3 Hz, 2H; Ar), 7.35–7.20 (m, 8H; Ar), 5.98 (s, 1H; 21H), 5.58 (s, 1H; OC*H*PhO), 5.06 (d, *J* = 11.5 Hz, 1H; C*H*HPh), 4.92 (d, *J* = 7.1 Hz, 1H; OC*H*HO), 4.79 (d, *J* = 7.1 Hz, 1H; OCH*H*O), 4.70 (d, *J* = 11.5 Hz, 1H; CH*H*Ph), 4.45 (d, *J* = 2.3 Hz, 1H; H16), 4.38 (d, *J* = 12.7 Hz, 1H; H14), 4.12 (d, *J* = 12.7 Hz, 1H; H14), 3.85 (s, 1H; H15), 3.75 (d, *J* = 2.3 Hz, 1H; H17), 3.46 (s, 3H; OMe), 3.14 (d, *J* = 16.8 Hz, 1H; H22), 2.89 ppm (d, *J* = 16.8 Hz, 1H; H22); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (s), 138.4 (s), 137.5 (s), 129.0 (d), 128.2 (4×d), 127.4 (d), 127.3 (2×d), 126.5 (2×d), 104.8 (d), 101.4 (d), 96.1 (t), 76.5 (d), 76.3 (s), 71.3 (d), 70.2 (t), 69.4 (t), 65.3 (d), 56.2 (q), 40.7 ppm (t); IR (film): ν_{max} = 3050, 2990, 1790, 1260, 1170, 1120, 1030 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{24}H_{27}O_8$: 443.1706; foudn: 443.1727 [*M*+H$^+$], Δ = 4.7 ppm.

(3a*S*,4*S*,5*S*,6*R*,7a*R*)-3a-Benzyloxy-5-hydroxy-6-hydroxymethyl-4-methoxymethoxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (47a): A mixture of trifluoroacetic acid (3 mL, 40.4 mmol) and water (3 mL, 166 mmol) was added to a solution of benzylidene acetal **47** (3.46 g, 7.8 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred vigorously at room temperature until TLC analysis indicated complete conversion. The reaction mixture was neutralised with NEt_3 (10 mL) and the mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (75% ethyl acetate in petrol) to yield diol **47a** (2.68 g, 97%) as a pale yellow oil. $[\alpha]_D$ = +1.2 (*c* = 0.48 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5H; Ph), 5.82 (s, 1H; H21), 5.08 (d, *J* = 11.4 Hz, 1H; C*H*HPh), 4.95 (d, *J* = 7.0 Hz, 1H; OC*H*HO), 4.80 (d, *J* = 7.0 Hz, 1H; OCH*H*O), 4.65 (d, *J* = 11.4 Hz, 1H; CH*H*Ph), 4.17 (d, *J* = 2.3 Hz, 1H; H16), 3.94–3.83 (m, 3H; H14, H15), 3.68 (d, *J* = 2.3 Hz, 1H; H17), 3.50 (s, 3H; OMe), 3.08 (d, *J* = 16.3 Hz, 1H; H22), 2.89 ppm (d, *J* = 16.3 Hz, 1H; H22); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.1 (s), 137.2 (s), 128.5 (2×d), 128.1 (d), 127.4 (2×d), 103.7 (d), 95.2 (t), 78.5 (s), 75.4 (d), 74.4 (d), 71.0 (t), 66.3 (d), 62.0 (t), 56.1 (q), 37.8 ppm (t); IR (film): ν_{max} = 3490, 2950, 1790, 1270, 1220, 1170, 1120, 1040, 1020, 950, 910, 730 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{17}H_{22}NaO_8$: 377.1212; found: 377.1229 [*M*+Na$^+$], Δ = 4.5 ppm.

(3a*S*,4*S*,5*S*,6*R*,7a*R*)-3a-Benzyloxy-6-(*tert*-butyldimethylsilyloxymethyl)-5-hydroxy-4-methoxymethoxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (47b): *N*,*N*-Dimethylaminopyridine (51.7 mg, 0.42 mmol), NEt_3 (1.77 mL, 12.7 mmol) and *tert*-butylchlorodimethylsilane (766 mg, 5.08 mmol) was added to a stirred solution of diol **47a** (1.50 g, 4.23 mmol) in DMF (70 mL). The reaction mixture was stirred at room temperature for 3 h then diluted with diethyl ether (50 mL) and the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (50 mL). The mixture was extracted with diethyl ether (3×50 mL) and the combined organic layers were washed with aqueous LiCl (10% wt/vol, 3×100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (0% then 20% ethyl acetate in petrol) to afford secondary alcohol **47b** (1.40 g, 71%) as a colourless oil. $[\alpha]_D$ = −8.3 (*c* = 0.54 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5H; Ph), 5.75 (s, 1H; H21), 5.11 (d, *J* = 11.4 Hz, 1H; C*H*HPh), 4.95 (d, *J* = 6.9 Hz, 1H; OC*H*HO), 4.80 (d, *J* = 6.9 Hz, 1H; OCH*H*O), 4.63 (d, *J* = 11.4 Hz, 1H; CH*H*Ph), 4.16 (br, 1H; H16), 3.91 (dd, *J* = 9.2, 7.1 Hz, 1H; H14), 3.82–3.87 (m, 1H; H15), 3.78 (dd, *J* = 9.2, 5.2 Hz, 1H; H14), 3.65 (d, *J* = 2.5 Hz, 1H; H17), 3.50 (s, 3H; OMe), 3.20 (br, 1H; OH), 3.09 (d, *J* = 16.5 Hz, 1H; H22), 2.84 (d, *J* = 16.5 Hz, 1H; H22), 0.89 (s, 9H; *t*BuSi), 0.08 (s, 3H; SiMe), 0.07 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.1 (s), 137.3 (s), 128.7 (2×d), 128.2 (d), 127.6 (2×d), 104.0 (d), 95.2 (t), 78.9 (s), 75.8 (d), 74.9 (d), 71.4 (t), 65.1 (d), 61.3 (t), 56.1 (q), 38.2 (t), 25.8 (3×q), 18.3 (s), −5.4 (q), −5.5 ppm (q); IR (film): ν_{max} = 3520, 2950, 2930, 2890, 2860, 1790, 1470, 1420, 1250, 1220, 1170, 1150, 1100, 1030, 950, 920, 780, 730 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{23}H_{36}NaO_8Si$: 491.2077; found: 491.2069 [*M*+Na$^+$], Δ = 1.6 ppm.

***O*-(3a*S*,4*S*,5*S*,6*R*,7a*R*)-3a-Benzyloxy-6-(*tert*-butyldimethylsilyloxymethyl)-4-methoxymethoxy-2-oxohexahydro-2*H*-furo[2,3-*b*]pyran-5-yl *S*-methyl carbonodithioate (48)**: Carbon disulfide (1.84 mL, 30.5 mmol) was added to a stirred solution of secondary alcohol **47b** (4.77 g, 10.2 mmol) in THF (370 mL) at −78 °C and the reaction mixture was stirred for 30 min. NaHMDS (1.0 M in THF, 11.2 mL, 11.2 mmol) was added and the reaction mixture stirred at −78 °C for 30 min. Methyl iodide (3.80 mL, 61.1 mmol) was added dropwise and the reaction mixture stirred for a further 30 min at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (40 mL) then allowed to reach room temperature. The mixture was extracted with diethyl ether (3×250 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (0–20% ethyl acetate in petrol) to yield xanthate **48** (5.26 g, 92%) as a

white crystalline solid. $[\alpha]_D = +62.8$ ($c = 1.13$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.37–7.31$ (m, 4H; Ph), 7.30–7.27 (m, 1H; Ph), 6.48 (d, $J = 2.2$ Hz, 1H; H16), 5.84 (s, 1H; H21), 5.00 (d, $J = 11.4$ Hz, 1H; CH*H*Ph), 4.99 (d, $J = 7.2$ Hz, 1H; OC*H*HO), 4.59 (d, $J = 11.4$ Hz, 1H; C*H*HPh), 4.59 (d, $J = 7.2$ Hz, 1H; OCH*H*O), 4.13 (m, 1H; H15), 3.90 (d, $J = 2.2$ Hz, 1H; H17), 3.74 (dd, $J = 10.0$, 5.8 Hz, 1H; H14), 3.66 (dd, $J = 10.0$, 7.9 Hz, 1H; H14), 3.48 (s, 3H; OMe), 3.09 (d, $J = 16.7$ Hz, 1H; H22), 2.85 (d, $J = 16.7$ Hz, 1H; H22), 2.43 (s, 3H; SMe), 0.86 (s, 9H; *t*BuSi), 0.03 (s, 3H; SiMe), 0.02 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 215.9$ (s), 169.1 (s), 138.2 (s), 128.4 (d), 127.8 (2×d), 127.6 (2×d), 104.6 (d), 95.1 (t), 77.3 (s), 74.6 (d), 73.1 (d), 71.7 (d), 70.8 (t), 60.7 (t), 56.6 (q), 39.7 (t), 25.8 (q), 18.7 (3×q), 18.2 (s), −5.5 (q), −5.6 ppm (q); IR (film): $\nu_{max} = 2950$, 2930, 2890, 2860, 1800, 1260, 1220, 1170, 1140, 1110, 1070, 1040 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{25}H_{39}O_8S_2Si$: 559.1856; found: 559.1860 [$M+H^+$], $\Delta = 0.7$ ppm; elemental analysis calcd (%) for $C_{25}H_{38}O_8SiS_2$: C 53.8, H 6.9; found: C 54.0, H 6.9.

(3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-(*tert*-butyldimethylsilyloxymethyl)-4-methoxymethoxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (49): Argon was bubbled through a stirred solution of xanthate **48** (4.20 g, 7.52 mmol), tributyltin hydride (6.07 mL, 22.5 mmol) and AIBN (62 mg, 0.38 mmol) in toluene (180 mL) for 30 min at room temperature. The reaction mixture was heated under reflux for 2 h then cooled to room temperature and the solvents removed in vacuo. The crude mixture was purified by flash column chromatography (0% to remove tin byproducts then 15% ethyl acetate in petrol) to yield **49** (3.40 g, quantitative) as a colourless oil. $[\alpha]_D = -8.1$ ($c = 1.09$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.29–7.25$ (m, 4H; Ph), 7.23–7.18 (m, 1H; Ph), 5.67 (s, 1H; H21), 4.91 (d, $J = 11.7$ Hz, 1H; C*H*HPh), 4.72 (d, $J = 6.9$ Hz, 1H; OC*H*HO), 4.63 (d, $J = 6.9$ Hz, 1H; OCH*H*O), 4.55 (d, $J = 11.7$ Hz, 1H; CH*H*Ph), 3.89–3.82 (m, 1H; H15), 3.73–3.70 (m, 1H; H17), 3.69 (dd, $J = 10.7$, 4.6 Hz, 1H; H14), 3.61 (dd, $J = 10.7$, 5.1 Hz, 1H; H14), 3.35 (s, 3H; OMe), 2.96 (d, $J = 16.7$ Hz, 1H; H22), 2.75 (d, $J = 16.7$ Hz, 1H; H22), 1.97–1.91 (m, 2H; 2×H16), 0.83 (s, 9H; *t*BuSi), 0.00 ppm (s, 6H; $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9$ (s), 138.3 (s), 128.3 (2×d), 127.5 (d), 126.9 (2×d), 104.9 (d), 95.5 (t), 77.1 (s), 76.0 (d), 72.9 (d), 69.7 (t), 65.0 (t), 55.7 (q), 38.2 (t), 28.2 (t), 25.7 (3×q), 18.2 (s), −5.4 (q), −5.4 ppm (q); IR (film): $\nu_{max} = 2950$, 2930, 2890, 2860, 1790, 1260, 1170, 1100, 1030, 950, 910 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{23}H_{36}NaO_7Si$: 475.2128; found: 475.2133 [$M+Na^+$], $\Delta = 1.1$ ppm.

(3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-hydroxymethyl-4-methoxymethoxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (49a): A mixture of trifluoroacetic acid (1 mL, 13.4 mmol) and water (1 mL, 55.5 mmol) was added to a vigourously stirred solution of silyl ether **49** (480 mg, 1.06 mmol) in CH_2Cl_2 (25 mL). When the reaction was deemed complete, NEt_3 (2 mL) was added and the mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (25% ethyl acetate in petrol) to yield primary alcohol **49a** (289 mg, 81%) as a colourless oil. $[\alpha]_D = -0.1$ ($c = 0.24$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.37–7.26$ (m, 5H; Ph), 5.75 (s, 1H; H21), 4.97 (d, $J = 11.7$ Hz, 1H; C*H*HPh), 4.79 (d, $J = 7.1$ Hz, 1H; OC*H*HO), 4.71 (d, $J = 7.1$ Hz, 1H; OCH*H*O), 4.59 (d, $J = 11.7$ Hz, 1H; CH*H*Ph), 3.99–3.94 (m, 1H; H15), 3.80 (dd, $J = 11.5$, 4.1 Hz, 1H; H17), 3.71 (dd, $J = 12.0$, 3.2 Hz, 1H; H14), 3.64 (dd, $J = 12.0$, 5.6 Hz, 1H; H14), 3.42 (s, 3H; OMe), 3.11 (br, 1H; OH), 3.03 (d, $J = 16.7$ Hz, 1H; H22), 2.83 (d, $J = 16.7$ Hz, 1H; H22), 2.05 (ddd, $J = 12.9$, 11.5, 10.6 Hz, 1H; H16), 1.90 ppm (ddd, $J = 12.9$, 4.1, 2.3 Hz, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 170.0$ (s), 138.1 (s), 128.4 (2×d), 127.7 (d), 127.1 (2×d), 104.8 (d), 95.7 (t), 77.2 (s), 75.9 (d), 72.9 (d), 70.0 (t), 64.7 (t), 55.9 (q), 38.1 (t), 27.6 ppm (t); IR (film): $\nu_{max} = 3460$, 2980, 2930, 1790, 1270, 1170, 1140, 1100, 1040, 1030 cm^{-1}.

(3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-(2′,2′-dibromovinyl)-4-methoxymethoxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (49c): iPr_2NEt (5.4 mL, 30.8 mmol) was added to a stirred solution of secondary alcohol **49a** (2.6 g, 7.7 mmol) in CH_2Cl_2 (230 mL) at room temperature. The mixture was cooled to 0°C and then a solution of SO_3·pyridine (3.67 g, 23.1 mmol) in dimethylsulfoxide (16 mL) was added drop wise. The reaction mixture was stirred at 0°C for 2 h and then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and allowed to reach room temperature. The mixture was extracted with CH_2Cl_2 (3×100 mL) and the organic layers combined, washed with saturated aqueous $CuSO_4$ (2×100 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude aldehyde **49b**. Potassium *tert*-butoxide (2.38 mg, 21.2 mmol) was added to a stirred solution of dibromomethyltriphenylphosphonium bromide (11.9 g, 23.1 mmol) in THF (75 mL). The mixture was stirred for a period of 10 min over which time the colour changed from yellow to dark brown. A solution of the crude aldehyde **49b** (ca. 2.29 mmol) in THF (115 mL) was added and the reaction mixture stirred at room temperature for 12 h. The reaction mixture was diluted with ether (250 mL) and the resulting precipitate was removed by filtration. The organic layers were concentrated in vacuo and the crude product was purified by flash column chromatography (5% ethyl acetate in petrol) to yield dibromoolefin **49c** (2.97 g, 78%) as a yellow oil. $[\alpha]_D = -25.5$ ($c = 1.30$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.39–7.27$ (m, 5H; Ph), 6.56 (d, $J = 7.6$ Hz, 1H; H14), 5.71 (s, 1H; H21), 4.99 (d, $J = 11.7$ Hz, 1H; C*H*HPh), 4.81 (d, $J = 6.9$ Hz, 1H; OC*H*HO), 4.72 (d, $J = 6.9$ Hz, 1H; OCH*H*O), 4.61 (d, $J = 11.7$ Hz, 1H; CH*H*Ph), 4.58 (ddd, $J = 10.4$, 7.6, 3.3 Hz, 1H; H15), 3.81 (dd, $J = 10.8$, 4.8 Hz, 1H; H17), 3.44 (s, 3H; OMe), 3.06 (d, $J = 16.6$ Hz, 1H; H22), 2.84 (d, $J = 16.6$ Hz, 1H; H22), 2.12–1.99 ppm (m, 2H; 2×H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 169.6$ (s), 138.1 (s), 136.2 (d), 128.5 (2×d), 127.8 (d), 127.1 (2×d), 104.4 (d), 95.8 (t), 93.1 (s), 76.8 (s), 75.5 (d), 73.1 (d), 70.2 (t), 56.1 (q), 38.1 (t), 29.9 ppm (t); IR (film): $\nu_{max} = 2940$, 1790, 1630, 1270, 1170, 1110, 1040, 950, 900, 720 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{18}H_{20}Br_2NaO_6$: 512.9524; found: 512.9519 [$M+Na^+$], $\Delta = 1.0$ ppm.

(3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-(2′,2′-dibromovinyl)-4-hydroxyhexahydro-2*H*-furo[2,3-*b*]pyran-2-one (57): Bromotrimethylsilane (0.253 mL, 1.9 mmol) was added to a stirred solution of MOM ether **49c** (377 mg, 0.77 mmol) in CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was stirred for 30 min and then the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL). The mixture was extracted with CH_2Cl_2 (3×30 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography (20–50% diethyl ether in petrol) to yield secondary alcohol **57** (343 mg, quantitative) as a colourless oil. $[\alpha]_D = -44.2$ ($c = 1.25$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.42–7.30$ (m, 5H; Ph), 6.56 (d, $J = 7.6$ Hz, 1H; H14), 5.86 (s, 1H; H21), 4.70 (d, $J = 11.3$ Hz, 1H; C*H*HPh), 4.66 (d, $J = 11.3$ Hz, 1H; CH*H*Ph), 4.57 (ddd, $J = 10.6$, 7.6, 2.8 Hz, 1H; H15), 3.79 (ddd, $J = 10.4$, 9.6, 4.3 Hz, 1H; H17), 2.94 (s, 2H; H22), 2.50 (d, $J = 9.6$ Hz, 1H; OH), 1.89 (ddd, $J = 13.1$, 10.6, 10.4 Hz, 1H; H16), 1.89 ppm (ddd, $J = 13.1$, 4.3, 2.8 Hz, 1H; H16); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.5$ (s), 136.7 (s), 136.2 (d), 128.8 (2×d), 128.4 (d), 127.3 (2×d), 101.2 (d), 93.2 (s), 77.0 (s), 72.3 (d), 68.7 (d), 67.6 (t), 35.6 (t), 32.6 ppm (t); IR (film): $\nu_{max} = 3510$, 3040, 2930, 1790, 1270, 1250, 1170, 1130, 1090, 1040, 950, 910, 740 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{16}H_{16}Br_2NaO_5$: 468.9262; found: 468.9270 [$M+Na^+$], $\Delta = 1.7$ ppm.

(3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-(2′,2′-dibromovinyl)-4-*para*-methoxybenzyloxy-hexahydro-2*H*-furo[2,3-*b*]pyran-2-one (76): To a solution of **57** (0.20 g, 0.45 mmol) in toluene (10 mL) was added *para*-methoxybenzyl-1,1,1-trichloroacetimidate (0.34 g, 1.35 mmol) followed by lanthanum(III) triflate (0.02 g, 0.045 mmol) and the resulting mixture stirred at room temperature for 3 h. The reaction was then partitioned between ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL), the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography afforded the title compound **76** as a colourless oil (0.23 g, 90%). $[\alpha]_D = -12.9$ ($c = 1.20$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.33–7.21$ (m, 7H; Ar), 6.88 (d, $J = 8.4$ Hz, 2H; Ar), 6.55 (d, $J = 7.5$ Hz, 1H; H14), 5.64 (s, 1H; H21), 4.95 (d, $J = 11.6$ Hz, 1H; C*H*HAr), 4.70 (d, $J = 11.4$ Hz, 1H; C*H*HPh), 4.53 (d, $J = 11.6$ Hz, 1H; CH*H*Ar), 4.51–4.50 (m, 1H; H17), 4.40 (d, $J = 11.4$ Hz, 1H; CH*H*Ph), 3.80 (s, 3H; OMe), 3.60 (dd, $J = 11.3$, 3.8 Hz, 1H; H15), 2.88 (d, $J = 16.6$ Hz, 1H; H22), 2.73 (d, $J = 16.6$ Hz, 1H; H22), 2.07 (app. dt, $J = 11.3$, 3.2 Hz, 1H; H16), 1.97 ppm (m, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 169.8$ (s), 159.6 (s), 138.2 (s), 136.5 (d), 129.5 (2×d), 129.1 (s), 128.4 (2×d), 127.7 (d), 127.3 (2×d), 114.1 (2×d), 104.5 (d), 92.6 (s), 77.2 (s), 76.0 (d), 73.3 (d), 71.3 (t), 70.3 (t), 55.3 (q), 38.1 (t), 28.7 ppm (t); IR (film): $\nu_{max} = 2925$, 1790, 1730, 1610, 1510, 1250, 1130, 1140, 950, 910 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{24}{}^{81}Br^{79}BrO_6$: 586.0263; found: 586.0254 [$M+NH_4^+$], $\Delta = 1.5$ ppm.

(2*R*,3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-(2′,2′-dibromovinyl)-2-methoxy-4-*para*-methoxybenzyloxyhexahydrofuro[2,3-*b*]pyran (23α-77) and (2*S*,3a*S*,4*S*,6*S*,7a*R*)-3a-benzyloxy-6-(2′,2′-dibromovinyl)-2-methoxy-4-*para*-methoxybenzyloxyhexahydro-uro[2,3-*b*]pyran (23β-77): To a solution of PMB ether **76** (0.30 g, 0.53 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added DIBAL-H (1.0 M in hexanes, 0.60 mL, 0.60 mmol) and the reaction stirred for 1 h. TLC analysis indicated that the reaction was incomplete and therefore further DIBAL-H was added (0.20 mL, 0.20 mmol) and the reaction stirred for 1 h before quenching with MeOH (1 mL). The reaction was then allowed to warm to room temperature and saturated aqueous sodium, potassium tartrate solution added, after which stirring was continued for 12 h. The product was extracted with CH_2Cl_2 (3× 50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo to afford the corresponding lactol as a colourless oil (0.29 g, 97 %) that was used without purification in the subsequent step. To a solution of the lactol (0.29 g, 0.51 mmol) in acetonitrile (22 mL) was added 3 Å molecular sieves (0.54 g), Amberlyst 15 (0.54 g) and MeOH (2.2 mL). The reaction was stirred for 16 h at room temperature, filtered through Celite and then concentrated in vacuo. Column chromatography afforded epimer 23α-**77** (0.150 g, 49 %) and 23β-**77** (0.077 g, 25 %) as colourless oils. 23α-**77**: $[\alpha]_D = -13.0$ ($c = 0.74$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.33$–7.25 (m, 7H; Ar), 6.91 (d, $J = 8.4$ Hz, 2H; Ar), 6.59 (d, $J = 7.5$ Hz, 1H; H14), 5.36 (s, 1H; H21), 4.95 (d, $J = 11.8$ Hz, 1H; C*H*HAr), 4.76–4.74 (m, 2H; H23, C*H*HPh), 4.57–4.53 (m, 2H; H15, CH*H*Ar), 4.41 (d, $J = 11.7$ Hz, 1H; CH*H*Ph), 3.82 (s, 3H; OMe), 3.52 (dd, $J = 11.6$, 3.5 Hz, 1H; H17), 3.39 (s, 3H; OMe), 2.54 (dd, $J = 13.5$, 6.3 Hz, 1H; H22), 2.03–1.98 (m, 2H; H22, H16), 1.91 ppm (app. q, $J = 12.0$ Hz, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.5$ (s), 139.2 (s), 138.0 (d), 129.9 (s), 129.6 (2×d), 128.2 (2×d), 127.3 (3×d), 113.9 (2×d), 102.8 (d), 100.9 (d), 91.0 (s), 78.1 (s), 77.0 (d), 72.7 (d), 70.8 (t), 69.7 (t), 55.8 (q), 55.3 (q), 36.9 (t), 28.6 ppm (t); IR (film): $\nu_{max} = 2926$, 1612, 1513, 1248, 1111, 1028 cm^{-1}. 23β-**77**: $[\alpha]_D = +11.9$ ($c = 0.65$ in $CHCl_3$); 7.32–7.26 (m, 7H; Ar), 6.87 (d, $J = 8.5$ Hz, 2H; Ar), 6.67 (d, $J = 7.7$ Hz, 1H; H14), 5.34 (s, 1H; H21), 5.05 (dd, $J = 4.8$, 2.8 Hz, 1H; H23), 4.88 (d, $J = 11.7$ Hz, 1H; C*H*HAr), 4.66 (d, $J = 11.2$ Hz, 1H; C*H*HPh), 4.60–4.58 (m, 2H; CH*H*Ar, H15), 4.52 (d, $J = 11.2$ Hz, 1H; CH*H*Ph), 4.20 (dd, $J = 10.4$, 4.1 Hz, 1H; H17), 3.81 (s, 3H; OMe), 3.39 (s, 3H; OMe), 2.32–2.31 (m, 2H; 2×H22), 2.00 (app. dt, $J = 15.5$, 4.1 Hz, 1H; H16), 1.94–1.93 ppm (m, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.2$ (s), 139.2 (s), 137.8 (d), 130.3 (s), 129.5 (2×d), 128.2 (2×d), 127.3 (d), 127.2 (2×d), 113.9 (2×d), 105.2 (d), 102.2 (d), 91.2 (s), 77.5 (s), 77.0 (d), 72.0 (d), 71.5 (t), 68.8 (t), 55.6 (q), 55.3 (q), 38.1 (t), 29.6 ppm (t); IR (film): $\nu_{max} = 2927$, 1613, 1513, 1454, 1248, 1098, 1029 cm^{-1}.

(2*R*,3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-ethynyl-2-methoxy-4-*para*-methoxybenzyloxyhexahydrofuro[2,3-*b*]pyran (23α-78): Methyl lithium/lithium bromide complex (1.50 M in diethyl ether, 0.165 mL, 0.25 mmol) was added dropwise to a solution of dibromoolefin 23α-**77** (30 mg, 0.051 mmol) in THF (2 mL) at −78 °C. After 1 h TLC indicated incomplete conversion so a further portion of methyl lithium/lithium bromide complex (0.165 mL, 0.26 mmol) was added and the reaction stirred for 1 h. The reaction was quenched with MeOH (0.2 mL), allowed to warm to room temperature and poured onto H_2O (20 mL). Diethyl ether (20 mL) was added and the organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to afford 23α-**78** as a colourless oil (21 mg, 97 %). $[\alpha]_D = -3.8$ ($c = 0.20$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.33$–7.23 (m, 7H; Ar), 6.91 (d, $J = 8.4$ Hz, 2H; Ar), 5.40 (s, 1H; H21), 4.94 (d, $J = 11.8$ Hz, 1H; C*H*HAr), 4.76–4.71 (m, 2H; C*H*HAr, H23), 4.63 (d, $J = 11.4$ Hz, 1H; H15), 4.58 (d, $J = 11.8$ Hz, 1H; CH*H*Ar), 4.39 (d, $J = 11.8$ Hz, 1H; CH*H*Ar), 3.82 (s, 3H; ArOMe), 3.48 (dd, $J = 11.5$, 3.6 Hz, 1H; H17), 3.37 (s, 3H; OMe), 2.49 (dd, $J = 13.5$, 6.2 Hz, 1H; H22), 2.48 (s, 1H; H13), 2.26 (app. q, $J = 12.0$ Hz, 1H; H16), 2.13 (dt, $J = 12.8$, 3.1 Hz, 1H; H16), 1.99 ppm (dd, $J = 13.5$, 4.5 Hz, 1H; H22); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.4$ (s), 139.2 (s), 129.8 (s), 129.5 (2×d), 128.1 (2×d), 127.2 (d), 127.1 (2×d), 113.9 (2×d), 102.7 (d), 101.0 (d), 81.4 (s), 78.5 (s), 76.9 (d), 73.3 (s), 70.6 (t), 69.4 (t), 61.8 (d), 55.8 (q), 55.3 (q), 36.9 (t), 31.1 ppm (t); IR (film): $\nu_{max} = 2942$, 1514, 1250, 1106, 1050 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{25}H_{28}O_6Na$: 447.1784; found: 447.1780 [*M*+Na^+], Δ = 0.4 ppm.

(2*S*,3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-6-ethynyl-2-methoxy-4-*para*-methoxybenzyloxyhexahydrofuro[2,3-*b*]pyran (23β-78): Methyl lithium/lithium bromide complex (1.50 M in diethyl ether, 1.83 mL, 2.74 mmol) was added dropwise to a solution of dibromoolefin 23β-**77** (0.320 g, 0.548 mmol) in THF (5.5 mL) at −78 °C. The reaction was then allowed to warm to −20 °C and maintained at this temperature for a further 3 h. The reaction was quenched with MeOH (1.0 mL), allowed to warm to room temperature and poured onto H_2O (40 mL). Diethyl ether (40 mL) was added and the organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (20 % diethyl ether in hexanes) afforded the title compound 23β-**78** as a colourless oil (0.215 g, 93 %). $[\alpha]_D = +63.5$ ($c = 0.14$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.30$–7.22 (m, 7H; Ar), 6.87 (d, 2H; $J = 9.3$ Hz, 2H; Ar), 5.45 (s, 1H; H21), 5.08 (d, $J = 5.6$ Hz, 1H; H23), 4.84 (d, $J = 11.8$ Hz, 1H; C*H*HAr), 4.75–4.65 (m, 2H; C*H*HPh, H15), 4.59 (d, $J = 11.8$ Hz, 1H; CH*H*Ar), 4.49 (d, $J = 11.3$ Hz, 1H; CH*H*Ph), 4.13 (dd, $J = 9.6$, 4.0 Hz, 1H; H17), 3.81 (s, 3H; OMe), 3.39 (s, 3H; OMe), 2.46 (s, 1H; H13), 2.33 (dd, $J = 13.5$, 5.6 Hz, 1H; H22), 2.25–2.18 (m, 2H; H22, H16), 2.13 ppm (app. dt, $J = 13.4$, 4.0 Hz, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.2$ (s), 139.4 (s), 130.3 (s), 129.3 (2×d), 128.2 (2×d), 127.2 (3×d), 113.8 (2×d), 104.5 (d), 103.3 (d), 81.7 (s), 78.7 (s), 76.6 (d), 73.4 (d), 71.3 (t), 68.3 (t), 61.1 (d), 55.8 (q), 55.3 (q), 38.2 (t), 31.3 ppm (t), 1×s not observed; IR (film): $\nu_{max} = 2965$, 1515, 1215, 1250, 1080 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{25}H_{28}O_6Na$: 447.1784; found: 447.1789 [*M*+Na^+], Δ = 1.1 ppm.

3-[(2*R*,3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-2-methoxy-4-*para*-methoxybenzyloxy-hexahydro-furo[2,3-*b*]pyran-6-yl]-prop-2-yn-1-ol (23α-79): Isopropyl magnesium bromide (2.0 M in THF, 0.112 mL, 0.224 mmol) was added to a solution of alkyne 23α-**78** (0.020 g, 0.047 mmol) in THF (1 mL) and the mixture was heated at 45 °C. After 30 min paraformaldehyde (0.020 g, 0.188 mmol) was added in a single portion. The reaction was then heated at 45 °C for 1.5 h before cooling to room temperature and quenching with saturated aqueous NH_4Cl solution (0.2 mL). Diethyl ether (10 mL) and water (10 mL) were then added, the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (25–50 % ethyl acetate in hexanes) afforded the title compound 23α-**79** as a colourless oil (0.019 mg, 89 %). $[\alpha]_D = +6.6$ ($c = 0.045$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$–7.26 (m, 7H; Ar), 6.91 (d, $J = 8.4$ Hz, 2H; Ar), 5.39 (s, 1H; H21), 4.94 (d, $J = 11.8$ Hz, 1H; C*H*HAr), 4.74–4.72 (m, 2H; C*H*HPh, H23), 4.67 (d, $J = 10.8$ Hz, 1H; H15), 4.58 (d, $J = 11.8$ Hz, 1H; CH*H*Ar), 4.39 (d, $J = 11.8$ Hz, 1H; CH*H*Ph), 4.29–4.28 (m, 2H; H18), 3.82 (s, 3H; OMe), 3.47 (dd, $J = 11.5$, 3.7 Hz, 1H; H17), 3.37 (s, 3H; OMe), 3.31 (m, 1H; OH), 2.49 (dd, $J = 13.2$, 6.0 Hz, 1H; H22), 2.21 (app. q, $J = 12.0$ Hz, 1H; H16), 2.11 (app. dt, $J = 12.6$, 3.0 Hz, 1H; H16), 1.99 ppm (dd, $J = 13.2$, 4.8 Hz, 1H; H22); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.4$ (s), 139.2 (s), 129.8 (s), 129.4 (2×d), 128.1 (2×d), 127.2 (3×d), 113.9 (2×d), 102.8 (d), 101.1 (d), 83.6 (s), 83.4 (s), 78.1 (s), 76.9 (d), 70.6 (t), 69.4 (t), 62.1 (d), 55.7 (q), 55.3 (q), 51.0 (t), 36.9 (t), 31.1 ppm (t); IR (film): $\nu_{max} = 2933$, 1513, 1248, 1104, 1027 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{30}O_7Na$: 447.1889; found: 447.1891 [*M*+Na^+], Δ = 0.3 ppm.

3-[(2*S*,3a*S*,4*S*,6*S*,7a*R*)-3a-Benzyloxy-2-methoxy-4-*para*-methoxybenzyloxy-hexahydrofuro[2,3-*b*]pyran-6-yl]-prop-2-yn-1-ol (23β-79): Isopropyl magnesium bromide (2.0 M in THF, 0.084 mL, 0.168 mmol) was added to a solution of alkyne 23β-**78** (15 mg, 0.035 mmol) in THF (0.75 mL) and the mixture was heated at 45 °C. After 30 min paraformaldehyde (15 mg, 0.14 mmol) was added in a single portion. The reaction was then heated at 45 °C for 5 h before cooling to room temperature and quenching with saturated aqueous NH_4Cl solution (0.2 mL). Diethyl ether (10 mL) and water (10 mL) were then added, the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (25–50 % ethyl acetate in hexanes) afforded the title compound 23β-**79** as a colourless oil (13 mg, 78 %). $[\alpha]_D = +59.2$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30$–7.21 (m, 7H; Ar), 6.85 (d, $J = 8.7$ Hz, 2H; Ar), 5.41 (s, 1H; H21), 5.06 (dd, $J = 6.2$, 2.3 Hz, 1H; H23), 4.81 (d, $J = 11.6$ Hz, 1H; C*H*HAr), 4.71–4.70 (m, 1H; H15), 4.67 (d, $J = 11.3$ Hz, 1H; C*H*HPh), 4.56 (d, $J = 11.6$, 1H; CH*H*Ar), 4.47 (d, $J = 11.3$ Hz, 1H; CH*H*Ph), 4.21–4.20 (m, 2H; H18), 4.11 (dd, $J = 8.9$, 4.0 Hz, 1H; H17), 3.78 (s, 3H; OMe), 3.36 (s, 3H; OMe), 2.44 (brs, 1H; OH), 2.31 (dd, $J = 13.6$, 6.2 Hz, 1H; H22), 2.21–2.15 (m, 2H; H22, H16), 2.10 ppm (app. dt, $J = 13.5$, 4.0 Hz, 1H; H16); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.2$ (s),

139.2 (s), 130.2 (s), 129.5 (2×d), 128.2 (2×d), 127.2 (d), 127.1 (2×d), 113.8 (2×d), 104.2 (d), 103.4 (d), 83.9 (s), 83.4 (s), 78.9 (s), 76.1 (d), 71.1 (t), 68.0 (t), 61.3 (d), 55.9 (q), 55.2 (q), 51.0 (t), 37.9 (t), 31.1 ppm (t); IR (film): ν_{max} = 3441, 2935, 1514, 1248, 1096, 1028 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{30}O_7Na$: 447.1889; founnd: 447.1890 [M+Na^+], Δ= 0.1 ppm.

Methanesulfonic acid 3-[(2*R*,3a*S*,4*S*,6*S*,7a*R*)-3a-benzyloxy-2-methoxy-4-*para*-methoxybenzyloxyhexahydrofuro[2,3-*b*]pyran-6-yl]-prop-2-ynyl ester (23α-63): *i*Pr_2NEt (0.095 mL, 0.55 mmol) was added to a solution of propargylic alcohol 23α-**79** (52 mg, 0.11 mmol), in CH_2Cl_2 (2.5 mL) at 0 °C. Methanesulfonic acid anhydride (48 mg, 0.275 mmol) was then added and the reaction maintained at 0 °C for 30 min then poured into saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (45% ethyl acetate in hexanes) afforded the title compound 23α-**63** (55 mg, 90%) as a colourless oil. $[\alpha]_D$ = +3.8 (*c* = 0.65 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 7H; Ar), 6.91 (d, *J* = 8.4 Hz, 2H; Ar), 5.37 (s, 1H; H21), 4.93 (d, *J* = 11.8 Hz, 1H; C*H*HPh), 4.88–4.87 (m, 2H; 2×H18), 4.74–4.72 (m, 2H; C*H*HAr, H23), 4.69 (app. d, *J* = 10.8 Hz, 1H; H15), 4.57 (d, *J* = 11.8 Hz, 1H; CH*H*Ph), 4.40 (d, *J* = 11.6 Hz, 1H; CH*H*Ar), 3.82 (s, 3H; OMe), 3.49 (dd, *J* = 11.4, 3.6 Hz, 1H; H17), 3.37 (s, 3H; OMe), 3.09 (s, 3H; SO_2Me), 2.49 (dd, *J* = 13.5, 6.1 Hz, 1H; H22), 2.20 (app. q, *J* = 12.0 Hz, 1H; H16), 2.10 (m, 1H; H16), 2.00 ppm (dd, *J* = 13.5, 4.5 Hz, 1H; H22); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 159.5 (s), 139.1 (s), 129.7 (s), 129.5 (2×d), 128.2 (2×d), 127.3 (d), 127.2 (2×d), 114.0 (2×d), 102.8 (d), 101.2 (d), 87.5 (s), 78.2 (s), 77.3 (s), 76.8 (d), 70.8 (t), 69.4 (t), 61.8 (d), 57.5 (t), 55.8 (q), 55.3 (q), 39.1 (q), 36.8 (t), 30.8 ppm (t); IR (film): ν_{max} = 2918, 2850, 1734, 1514, 1456, 1249, 1177, 1101, 1027 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{32}O_9SNa$: 555.1665; found: 555.1647 [M+Na^+], Δ = 1.8 ppm.

Methanesulfonic acid 3-[(2*S*,3a*S*,4*S*,6*S*,7a*R*)-3a-benzyloxy-2-methoxy-4-*para*-methoxybenzyloxyhexahydrofuro[2,3-*b*]pyran-6-yl]-prop-2-ynyl ester (23β-63): *i*Pr_2NEt (0.018 mL, 0.11 mmol) was added to a solution of propargylic alcohol 23β-**79** (10 mg, 0.022 mmol), in CH_2Cl_2 (1.25 mL) at 0 °C. Methanesulfonic acid anhydride (9 mg, 0.055 mmol) was then added and the reaction maintained at 0 °C for 30 min then poured into saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (45% ethyl acetate in hexanes) afforded the title compound 23β-**63** (11 mg, 90%) as a colourless oil. $[\alpha]_D$ = +71.5 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 7H; Ar), 6.88 (d, *J* = 8.5 Hz, 2H; Ar), 5.39 (s, 1H; H21), 5.10 (dd, *J* = 6.1, 2.0 Hz, 1H; H23), 4.84 (m, 2H; 2×H18), 4.81 (d, *J* = 11.6 Hz, 1H; C*H*HAr), 4.80–4.76 (m, 1H; H15), 4.68 (d, *J* = 11.2 Hz, 1H; C*H*HPh), 4.56 (d, *J* = 11.6 Hz, 1H; CH*H*Ar), 4.49 (d, *J* = 11.2 Hz, 1H; CH*H*Ph), 4.14 (dd, *J* = 9.1, 3.8 Hz, 1H; H17), 3.81 (s, 3H; OMe), 3.40 (s, 3H; OMe), 3.05 (s, 3H; SO_2Me), 2.35 (dd, *J* = 13.6, 6.1 Hz, 1H; H22), 2.23–2.17 (m, 2H; H16, H22), 2.12 ppm (app. dt, *J* = 13.4, 4.0 Hz, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.3 (s), 139.0 (s), 130.0 (s), 129.4 (2×d), 128.2 (2×d), 127.3 (d), 127.1 (2×d), 113.8 (2×d), 104.2 (d), 103.7 (d), 87.8 (s), 79.2 (s), 77.5 (s), 75.9 (d), 71.4 (t), 68.0 (t), 61.1 (d), 57.6 (t), 56.0 (q), 55.3 (q), 39.0 (q), 37.7 (t), 30.7 ppm (t); IR (film): ν_{max} = 2918, 2850, 1734, 1514, 1456, 1249, 1177, 1101, 1027 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{32}O_9SNa$: 555.1665; found: 555.1650 [M+Na^+], Δ = 2.7 ppm.

Propargylic enol ether 23α-80: To a stirred solution of decalin ketone **21** (0.242 g, 0.338 mmol) in THF (1.5 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 0.013 g, 0.328 mmol). The reaction was then stirred for 30 min at 0 °C before [15]crown-5 (0.065 mL, 0.328 mmol) was added. After stirring for a further 30 min at 0 °C a solution of mesylate 23α-**63** (36 mg, 0.068 mmol) in THF (1 mL + 2×0.5 mL washings) was added drop wise. The reaction was then allowed to warm to room temperature and after 3 h was quenched by slow addition of saturated aqueous NH_4Cl solution (0.2 mL). The reaction mixture was then partitioned between ethyl acetate (20 mL) and water (20 mL) and the organic layer was separated, dried ($MgSO_4$) and the solvent removed in vacuo. Column chromatography (25–60% ethyl acetate in hexanes afforded the title compound 23α-**80** as a colourless oil (63 mg, 82%). $[\alpha]_D$ = +4.4 (*c* = 0.30 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 12H; Ar), 6.88 (d, *J* = 8.5 Hz, 2H; Ar), 5.37 (s, 1H; H21), 4.92 (d, *J* = 11.9 Hz, 1H; C*H*HPh), 4.73 (d, *J* = 11.7 Hz, 1H; C*H*HPh), 4.66 (app. t, *J* = 5.1 Hz, 1H; H23), 4.57–4.47 (m, 7H; 2×CH*H*Ph, CH_2Ar, H18, H6, H15), 4.43 (dd, *J* = 15.0, 1.0 Hz, 1H; H18), 4.33 (brs, 1H; H1), 4.10 (d, *J* = 8.0 Hz, 1H; H28), 3.97 (d, *J* = 8.0 Hz, 1H; H28), 3.87 (brs, 1H; H3), 3.82 (s, 3H; OMe), 3.78 (s, 3H; CO_2Me), 3.52 (s, 3H; CO_2Me), 3.46 (d, *J* = 9.5 Hz, 1H; H19), 3.41 (d, *J* = 9.5 Hz, 1H; H19), 3.38 (dd, *J* = 13.4, 5.7 Hz, 1H; H17), 3.35 (s, 3H; OMe), 2.90 (d, *J* = 11.8 Hz, 1H; H5), 3.24 (s, 1H; H9), 2.47 (dd, *J* = 13.5, 6.2 Hz, 1H; H22), 2.25 (d, *J* = 12.4 Hz, 1H; H2), 2.20–2.10 (m, 2H; 2×H16), 1.98–1.92 (m, 2H; H2, H22), 1.75 (s, 3H; 30Me), 0.94 (q, *J* = 5.6 Hz, 18H; $SiCH_2CH_3$), 0.60 ppm (m, 12H; $SiCH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.2 (s), 170.0 (s), 159.3 (s), 152.5 (s), 139.3 (s), 138.4 (s), 129.9 (s), 129.5 (2×d), 128.5 (2×d), 128.1 (2×d), 127.4 (d), 127.2 (2×d), 127.1 (3×d), 115.7 (s), 113.9 (2×d), 105.6 (s), 102.7 (d), 100.9 (d), 83.7 (s), 81.4 (s), 78.0 (s), 77.0 (d), 73.8 (t), 70.8 (d), 70.4 (d), 70.4 (t), 69.4 (t), 67.6 (t), 66.6 (d), 65.4 (t), 62.2 (d), 58.3 (t), 58.1 (d), 55.7 (q), 55.3 (q), 54.2 (s), 52.5 (q), 52.0 (q), 47.6 (s), 46.1 (d), 37.5 (t), 36.9 (t), 30.9 (t), 15.3 (q), 7.0 (3×q), 7.0 (3×q), 4.9 (3×t), 4.7 ppm (3×t); IR (film): ν_{max} = 2951, 1730, 1453, 1249, 1106 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{63}H_{90}O_{16}Si_2N$: 1172.5798; found: 1172.5741 [M+NH_4^+], Δ = 4.8 ppm.

Propargylic enol ether 23β-80: To a stirred solution of decalin ketone **21** (0.10 g, 0.139 mmol) in THF (0.5 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 5.4 mg, 0.133 mmol). The reaction was then stirred for 30 min at 0 °C before [15]crown-5 (0.027 mL, 0.136 mmol) was added. After stirring for a further 30 min at 0 °C a solution of mesylate 23β-**63** (14.8 mg, 0.028 mmol) in THF (0.5 mL + 2×0.25 mL washings) was added dropwise. The reaction was then allowed to warm to room temperature and after 3 h was quenched by slow addition of saturated aqueous NH_4Cl solution. The reaction mixture was then partitioned between ethyl acetate (10 mL) and water (10 mL) and the organic layer was separated, dried ($MgSO_4$) and the solvent removed in vacuo. Column chromatography (25–60% ethyl acetate in hexanes afforded the title compound 23β-**80** as a colourless oil (0.024 g, 74%). $[\alpha]_D$ = +33.4 (*c* = 1.25 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 12H, Ar), 6.86 (d, *J* = 8.5 Hz, 2H; Ar), 5.41 (s, 1H; H21), 5.03 (d, *J* = 4.7 Hz, 1H; H23), 4.85 (d, *J* = 11.7 Hz, 1H; C*H*HPh), 4.68 (d, *J* = 11.2 Hz, 1H; C*H*HPh), 4.64 (d, *J* = 6.7 Hz, 1H; H15), 4.58 (d, *J* = 11.8 Hz, 1H; CH*H*Ph), 4.56–4.40 (m, 5H; CH*H*Ph, CH_2Ar, 2×H18), 4.33 (brs, 1H; H1), 4.14–4.07 (m, 2H; H17, H28), 3.96 (d, *J* = 8.0 Hz, 1H; H28), 3.86 (brs, 1H; H3), 3.80 (s, 3H; OMe), 3.78 (s, 3H; CO_2Me), 3.52 (s, 3H; CO_2Me), 3.46 (d, *J* = 11.0 Hz, 1H; H19), 3.40 (d, *J* = 11.0 Hz, 1H; H19), 3.34 (s, 3H; OMe), 3.24 (s, 1H; H9), 2.90 (d, *J* = 11.7 Hz, 1H; H5), 2.31–2.21 (m, 3H; 2×H22, H2), 2.19–2.09 (m, 2H; 2×H16), 1.94 (d, *J* = 15.5 Hz, 1H; H2); 1.75 (s, 3H; 30Me), 0.97–0.92 (m, 18H; $SiCH_2CH_3$), 0.51–0.45 ppm (m, 12H; $SiCH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.7 (s), 170.1 (s), 159.6 (s), 153.0 (s), 139.8 (s), 138.8 (s), 130.9 (s), 129.8 (2×d), 128.7 (2×d), 128.6 (2×d), 127.8 (d), 127.6 (3×d), 127.5 (2×d), 127.5 (2×d), 114.3 (s), 108.1 (s), 105.0 (d), 102.8 (d), 84.5 (s), 81.9 (s), 78.6 (d), 77.1 (s), 74.2 (t), 71.1 (t), 70.8 (d), 70.5 (d), 68.9 (t), 68.1 (t), 67.1 (d), 65.9 (t), 61.9 (d), 58.8 (t), 58.5 (d), 56.0 (q), 55.7 (q), 54.7 (s), 52.9 (q), 52.4 (q), 45.7 (s), 43.7 (d), 38.8 (t), 38.0 (t), 31.8 (t), 15.7 (q), 7.4 (6×q), 5.6 (3×t), 5.2 ppm (3×t); IR (film): ν_{max} = 2627, 1733, 1174, 1087 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{63}H_{86}O_{16}Si_2Na$: 1177.5367; found: 1177.5347 [M+Na^+], Δ = 1.7 ppm.

Propargylic enol ether diol 23α-81: To a stirred solution of *bis* triethylsilylether 23α-**80** (0.050 g, 0.043 mmol) in THF (3.6 mL) at 0 °C was added TBAF (2.0 M in THF, 0.112 mL, 0.043 mmol). After 10 min the reaction was concentrated in vacuo and the crude residue purified by flash column chromatography on silica (0–3% MeOH in CH_2Cl_2) to afford diol 23α-**81** (0.035 mg, 90%) as a colourless oil. $[\alpha]_D$ = +10.6 (*c* = 0.45 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 12H; Ar), 6.90 (d, *J* = 8.4 Hz, 2H; Ar), 5.34 (s, 1H; H21), 4.93 (d, *J* = 11.3 Hz, 1H; C*H*HPh), 4.75 (d, *J* = 15.0 Hz, 1H; H18), 4.72 (d, *J* = 11.6 Hz, 1H; C*H*HPh), 4.68 (app. t, *J* = 5.1 Hz, 1H; H23), 4.62 (d, *J* = 11.4 Hz, 1H; H6), 4.60–4.51 (m, 5H; H18, CH*H*Ph, CH_2Ar, H15), 4.34 (d, *J* = 11.7 Hz, 1H; CH*H*Ph), 4.30 (brs, 1H; H1), 4.18 (d, *J* = 8.5 Hz, 1H; H28), 4.00 (d,

J=8.5 Hz, 1H; H28), 3.82 (s, 3H; OMe), 3.80 (s, 3H; CO_2Me), 3.75 (brs, 1H; H3), 3.65 (d, J=8.6 Hz, 1H; H19), 3.62 (brs, 1H; OH), 3.60 (s, 3H; CO_2Me), 3.55 (s, 1H; H9), 3.42 (d, J=10.2 Hz, 1H; H19), 3.38 (dd, J=11.9, 3.5 Hz, 1H; H17), 3.35 (s, 3H; OMe), 3.22 (brs, 1H; OH), 2.76 (d, J=11.5 Hz; H5), 2.47 (dd, J=13.4, 6.2 Hz, 1H; H22), 2.15 (app. q, J=12.0 Hz, 1H; H16), 2.07–1.95 (m, 4H; H16, 2×H2, H20), 1.77 ppm (s, 3H; 30Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.1 (s), 170.3 (s), 159.4 (s), 151.4 (s), 138.9 (s), 138.5 (s), 129.9 (s), 129.5 (2×d), 128.3 (2×d), 128.2 (2×d), 127.6 (2×d), 127.5 (d), 127.2 (d), 126.9 (2×d), 117.2 (s), 113.4 (2×d), 105.6 (s), 102.8 (d), 100.9 (d), 84.7 (s), 81.4 (s), 78.1 (s), 77.2 (d), 73.5 (t), 71.3 (d), 70.6 (t), 70.5 (d), 69.8 (t), 68.0 (t), 67.4 (d), 65.5 (t), 62.1 (d), 58.9 (t), 58.3 (d), 55.7 (q), 55.3 (q), 54.5 (s), 52.8 (q), 52.0 (q), 47.9 (s), 43.9 (d), 37.0 (t), 34.5 (t), 30.9 (t), 15.8 ppm (q); IR (film): ν_{max} = 3486, 2951, 1728, 1514, 1453, 1249, 1104 cm^{-1}; HRMS: m/z: calcd for $C_{51}H_{58}O_{16}Na$: 949.3623; found: 949.3592 [M+Na$^+$], Δ=3.3 ppm.

Propargylic enol ether diol 23β-81: To a stirred solution of bistriethylsilylether 23β-**80** (9 mg, 0.0078 mmol) in THF (0.6 mL) at 0°C was added TBAF (1.0 M in THF, 0.023 mL, 0.0234 mmol). After 10 min the reaction was concentrated in vacuo and the crude residue purified by flash column chromatography on silica gel (0–3% MeOH in CH_2Cl_2) to afford diol 23β-**81** (7 mg, quantitative) as a colourless oil. $[\alpha]_D$=+40.7 (c=0.89 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.30–7.26 (m, 12H; Ar), 6.87 (d, J=8.5 Hz, 2H, Ar), 5.36 (s, 1H; H21), 5.03 (d, J=4.9 Hz, 1H; H23), 4.86 (d, J=11.3 Hz, 1H; C*H*HPh), 4.74 (d, J=15.3 Hz, 1H; H18), 4.67 (d, J=11.2 Hz, 1H; C*H*HPh), 4.60–4.50 (m, 6H; CH*H*Ph, CH_2Ar, H18, H6, H15), 4.46 (d, J=11.2 Hz, 1H; CH*H*Ph), 4.33 (brs, 1H; H1), 4.18 (d, J=8.5 Hz, 1H; H28), 4.10 (app. d, J=8.4 Hz, 1H; H17), 4.01 (d, J=8.5 Hz, 1H; H28), 3.82 (brs, 1H; H3), 3.81 (s, 3H; OMe), 3.80 (s, 3H; CO_2Me), 3.65 (d, J=9.7 Hz, 1H; H19), 3.57 (s, 3H; OMe), 3.45–3.42 (m, 3H; H19, H9, OH), 3.07 (brs, 1H; OH), 2.75 (d, J=11.4 Hz, 1H; H5), 2.31 (dd, J=13.3, 7.2, 1H; H22), 2.25 (d, J=13.2 Hz, 1H; H22); 2.15–2.02 (m, 4H; 2×H16, 2×H2), 1.77 ppm (s, 3H; 30Me), ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.4 (s), 170.3 (s), 159.2 (s), 151.4 (s), 139.0 (s), 138.5 (s), 130.4 (s), 129.4 (2×d), 128.3 (2×d), 128.2 (2×d), 127.5 (2×d), 127.4 (d), 127.2 (d), 126.9 (2×d), 117.0 (s), 113.7 (2×d), 105.6 (s), 104.9 (d), 102.6 (d), 84.9 (s), 81.4 (s), 78.1 (s), 76.8 (d), 73.5 (t), 71.3 (t), 71.2 (d), 70.5 (d), 68.8 (t), 68.0 (t), 67.4 (d), 65.6 (t), 61.5 (d), 58.8 (t), 58.3 (d), 55.7 (q), 55.3 (q), 54.5 (s), 52.8 (q), 52.1 (q), 48.0 (s), 43.9 (d), 38.0 (t), 34.5 (t), 31.2 (t), 15.8 ppm (q); HRMS: m/z: calcd for $C_{51}H_{58}O_{16}Na$: 949.3643; found: 949.3617 [M+Na$^+$], Δ=2.8 ppm.

Allene diol 23α-82: Diol 23α-**81** (35 mg, 0.038 mmol) was placed into a base-washed microwave vial to which was added degassed 1,2-dichlorobenzene (2 mL). The resulting solution was then further degassed before subjecting to microwave heating (4×5 min at 185°C with 1 min cooling between each cycle). The reaction was then allowed to cool to room temperature prior to column chromatography (CH_2Cl_2 followed by 2% MeOH in CH_2Cl_2). The product 23α-**82** was isolated as a colourless oil (30 mg, 86%). $[\alpha]_D$=−10.0 (c=0.04 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.35–7.23 (m, 12H; Ar), 6.89 (d, J=8.5 Hz, 2H; Ar), 5.32 (s, 1H; H21), 4.96 (d, J=11.5 Hz, 1H; C*H*HPh), 4.93–4.91 (m, 3H; C*H*HPh, 2×H18), 4.74 (app. t, J=5.6 Hz, 1H; H23), 4.68 (d, J=11.7 Hz, 1H; C*H*HAr), 4.52 (d, J=11.9 Hz, 1H; CH*H*Ph), 4.47 (d, J=11.6 Hz, 1H; CH*H*Ph), 4.47–4.45 (m, 1H; H15), 4.39 (d, J=11.5 Hz, 1H; CH*H*Ar), 4.36 (brs, 1H; H1), 4.24 (d, J=14.0 Hz, 1H; H6), 4.03 (d, J=8.9 Hz, 1H; H28), 3.97 (brs, 1H; H3), 3.90 (d, J=8.2 Hz, 1H; H28), 3.82 (s, 3H; OMe), 3.70 (d, J=9.4 Hz, 1H; H19), 3.60 (s, 3H; CO_2Me), 3.59 (s, 1H; H9), 3.54–3.45 (m, 5H; H5, H17, H19, 2×OH), 3.44 (s, 3H; CO_2Me), 3.36 (s, 3H; OMe), 2.50 (dd, J=13.9, 6.7 Hz, 1H; H22), 2.25 (m, 1H; H2), 2.21–2.14 (m, 2H; H2, H16), 1.96 (dd, J=13.9, 4.6 Hz, 1H; H22), 1.87 (d, J=12.6 Hz, 1H; H16), 1.56 ppm (s, 3H; 30Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ=207.4 (s), 206.6 (s), 174.3 (s), 168.9 (s), 159.3 (s), 139.3 (s), 137.0 (s), 130.2 (s), 129.6 (2×d), 128.5 (2×d), 128.1 (2×d), 127.8 (d), 127.7 (2×d), 127.3 (2×d), 127.2 (d), 113.9 (2×d), 108.5 (s), 105.8 (s), 103.2 (d), 101.3 (d), 80.1 (t), 78.3 (d), 78.2 (s), 77.2 (d), 75.7 (d), 73.5 (d), 73.0 (t), 71.0 (t), 69.6 (t), 69.1 (t), 67.0 (d), 65.9 (t), 56.6 (d), 55.8 (q), 55.3 (q), 53.5 (s), 53.3 (s), 52.6 (q), 51.9 (q), 48.6 (s), 38.3 (d), 37.1 (t), 34.7 (t), 29.7 (t), 22.9 ppm (q); IR (film): ν_{max} = 2923, 2325, 1725, 1259, 1024 cm^{-1}; HRMS: m/z: calcd for $C_{51}H_{62}O_{16}N$: 944.4069; found: 944.4089 [M+NH$_4^+$], Δ=2.1 ppm.

Allene diol 23β-82: Diol 23β-**81** (12 mg, 0.013 mmol) was placed into a base washed microwave vial to which was added degassed 1,2-dichlorobenzene (0.3 mL). The resulting solution was then further degassed before subjecting to microwave heating (4×5 min at 185°C with 1 min cooling between each cycle). The reaction was then allowed to cool to room temperature prior to column chromatography on silica gel eluting with CH_2Cl_2 followed by 2% MeOH in CH_2Cl_2. The product 23β-**82** was isolated as a colourless oil (9.9 mg, 83%). $[\alpha]_D$=+13.3 (c=0.58 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.28–7.20 (m, 12H; Ar), 6.87 (d, J=8.5 Hz, 2H; Ar), 5.31 (s, 1H; H21), 5.01 (d, J=5.8 Hz, 1H; H23), 4.95 (d, J=11.8 Hz, 1H; C*H*HPh), 4.92–4.88 (m, 3H; C*H*HPh, 2×H18), 4.62 (d, J=11.2 Hz, 1H; C*H*HPh), 4.59 (d, J=11.7 Hz, 1H; CH*H*Ph), 4.55 (d, J=11.2 Hz, CH*H*Ph), 4.51 (brs, 1H; H15), 4.47 (d, J=11.7 Hz, 1H; CH*H*Ph), 4.35 (m, 1H; H1), 4.22 (d, J=14.5 Hz, 1H; H6), 4.17 (dd, J=11.3, 4.1 Hz, 1H; H17), 4.02 (d, J=8.1 Hz, 1H; H28), 3.97 (m, 1H; H3), 3.90 (d, J=8.2 Hz, 1H; H28), 3.81 (s, 3H; CO_2Me), 3.74 (brs, 1H; H9), 3.70 (d, J=9.5 Hz, 1H; H19), 3.65 (s, 3H; CO_2Me), 3.52 (d, J=9.5 Hz, 1H; H19), 3.48 (m, 2H; H5, OH), 3.43 (s, 3H; OMe), 3.40 (s, 3H; OMe), 3.29 (d, J=4.8 Hz, 1H; OH), 2.36–2.16 (m, 4H; 2×H22, 2×H2), 2.13–2.07 (m, 1H; H16), 1.81 (d, J=23.8 Hz, 1H; H16), 1.56 ppm (s, 3H; 30Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ=207.0 (s), 206.5 (s), 174.3 (s), 169.0 (s), 159.1 (s), 139.4 (s), 137.0 (s), 130.8 (s), 129.5 (2×d), 128.5 (2×d), 128.2 (d), 128.1 (d), 127.8 (d), 127.7 (2×d), 127.2 (2×d), 127.2 (d), 113.7 (2×d), 106.3 (s), 105.9 (s), 103.2 (d), 101.8 (d), 80.6 (t), 80.6 (d), 76.9 (s), 77.2 (d), 75.6 (d), 73.5 (d), 73.1 (t), 71.8 (t), 69.4 (t), 69.1 (t), 67.1 (d), 65.9 (t), 57.6 (d), 55.5 (q), 55.3 (q), 53.5 (s), 53.4 (s), 52.7 (q), 51.8 (q), 48.5 (s), 38.5 (d), 38.2 (t), 34.8 (t), 29.7 (t), 22.4 ppm (q); IR (film): ν_{max} = 2627, 1734, 1106 cm^{-1}; HRMS: m/z: calcd for $C_{63}H_{86}O_{16}Si_2Na$: 949.3623; found: 949.3617 [M+Na$^+$], Δ=2.8 ppm.

The yield over three steps starting from mesylate **63** is here 61%, however, if the material is carried forward over the three steps with column chromatography used only in the final step, the yield is then increased to 72% over three steps (starting from 0.03 mmol mesylate).

TBS ether 23α-82a: To a stirred solution of diol 23α-**82** (0.039 g, 0.042 mmol) in DMF (4 mL) was added *tert*-butyldimethylsilyl imidazole (0.080 mL, 0.42 mmol). The resulting solution was heated to 80°C for 2 h and then allowed to cool to room temperature. The reaction mixture was partitioned between ethyl acetate (20 mL) and saturated aqueous LiCl solution (20 mL) and the organic layer separated and further washed with saturated aqueous LiCl solution (3×10 mL). Column chromatography (25–50% ethyl acetate in hexanes) afforded the title compound 23α-**82a** as a colourless oil (0.039 g, 91%). $[\alpha]_D$=−13.3 (c=0.29 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.37–7.19 (m, 12H; Ar), 6.90 (d, J=8.5 Hz, 2H; Ar), 5.33 (brs, 1H; H21), 5.30 (d, J=11.7 Hz, 1H; C*H*HPh), 4.97 (d, J=11.3 Hz, 1H; H18), 4.88 (d, J=12.3 Hz, 1H; C*H*HPh), 4.83 (d, J=11.2 Hz, 1H; H18), 4.76 (app. t, J=4.8 Hz, 1H; H23), 4.69 (d, J=11.4 Hz, 1H; C*H*HAr), 4.57 (d, J=12.2 Hz, 1H; CH*H*Ph), 4.57 (m, 1H; H15), 4.50–4.48 (m, 2H; CH*H*Ph, H1), 4.31 (d, J=11.5 Hz, 1H; CH*H*Ar), 4.16 (d, J=14.2 Hz, 1H; H6), 3.88–3.84 (m, 2H; H3, H28), 3.82–3.80 (m, 7H; CO_2Me, OMe, H28), 3.61 (d, J=9.9 Hz, 1H; H19), 3.58 (dd, J=8.3, 3.9 Hz, 1H; H17), 3.52 (s, 1H; H9), 3.48–3.42 (m, 2H; H19, OH), 3.50 (s, 3H; CO_2Me), 3.38 (d, J=14.3 Hz, 1H; H5), 3.35 (s, 3H; OMe), 2.43 (dd, J=13.5, 6.2 Hz, 1H; H22), 2.24 (d, J=15.0 Hz, 1H; H2), 2.17 (d, J=15.6 Hz, 1H; H2), 1.99 (d, J=11.3 Hz, 1H; H16), 1.95 (dd, J=13.5, 4.5 Hz, 1H; H22), 1.86 (d, J=11.2 Hz, 1H; H16), 1.57 (s, 3H; 30Me), 0.90 (s, 9H; *t*BuSi),0.13 (s, 3H; SiMe), 0.09 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): δ=206.5 (s), 206.3 (s), 174.0 (s), 168.7 (s), 159.2 (s), 139.6 (s), 137.1 (s), 130.4 (s), 129.4 (4×d), 128.5 (2×d), 128.0 (2×d), 127.7 (d), 127.6 (2×d), 127.0 (d), 113.8 (2×d), 109.1 (s), 105.9 (s), 103.3 (d), 101.3 (d), 81.0 (t), 78.5 (d), 77.6 (s), 75.3 (d), 73.2 (d), 72.8 (t), 70.3 (t), 69.1 (t), 69.0 (t), 68.8 (d), 67.6 (d), 65.8 (t), 60.3 (s), 58.2 (d), 55.5 (q), 55.3 (q), 53.2 (s), 52.6 (q), 52.0 (q), 48.3 (s), 38.1 (d), 37.2 (t), 35.5 (t), 29.6 (t), 25.9 (3×q), 18.3 (q), 14.0 (s), −4.8 (q), −5.1 ppm (q); IR (film): ν_{max} = 1725, 1454, 1246, 1092, 841 cm^{-1}; HRMS: m/z: calcd for $C_{57}H_{72}O_{16}SiNa$: 1063.4487; found: 1063.4488 [M+Na$^+$], Δ=0.1 ppm.

TBS ether 23β-82a: To a stirred solution of diol 23β-**82** (49.4 mg, 0.053 mmol) in DMF (1 mL) was added *tert*-butyldimethylsilyl imidazole

(0.2 mL, 1.07 mmol). The resulting solution was heated to 80 °C for 2 h and then allowed to cool to room temperature. The reaction mixture was partitioned between ethyl acetate (20 mL) and saturated aqueous LiCl solution (20 mL) and the organic layer separated and further washed with saturated aqueous LiCl solution (3×10 mL). Column chromatography (10–50 % ethyl acetate in hexanes) afforded the title compound 23β-**82a** as a colourless oil (48.1 mg, 86 %). $[\alpha]_D = +14.6$ ($c = 0.79$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.27$–7.21 (m, 12H; Ar), 6.86 (d, $J =$ 8.5 Hz, 2H; Ar), 5.30 (brs, 1H; H21), 4.99–4.94 (m, 3H; H18, C*H*HPh, H23), 4.90 (d, $J = 12.0$ Hz, 1H; C*H*HPh), 4.84 (m, 1H; H18), 4.77–4.62 (m, 1H; H15), 4.65 (d, $J = 11.4$ Hz, 1H C*H*HPh), 4.59 (d, $J = 12.0$ Hz, 1H; CH*H*Ph), 4.50–4.42 (m, 3H; 2×CH*H*Ph, H1), 4.26 (dd, $J = 11.4$, 4.9 Hz, 1H; H17), 4.15 (d, $J = 14.2$ Hz, 1H; H6), 3.88–3.84 (m, 2H; H28, H3), 3.83–3.82 (m, 1H; H28), 3.81 (s, 3H; CO_2Me), 3.80 (s, 3H; OMe), 3.57–3.49 (m, 4H; 2×OH, 2×H19), 3.42 (d, $J = 13.7$ Hz, 1H; H5), 3.42 (s, 3H; OMe), 3.39 (s, 3H; CO_2Me), 2.31–2.22 (m, 3H; 2×H22, H2), 2.17 (d, $J =$ 15.5 Hz, 1H; H2), 1.93–1.91 (m, 2H; 2×H16), 1.63 (s, 3H; 30Me), 0.89 (s, 9H; *t*BuSi), 0.12 (s, 3H; SiMe), 0.07 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.5$ (s), 206.3 (s), 174.1 (s), 168.8 (s), 159.0 (s), 139.8 (s), 137.8 (s), 131.0 (s), 129.1 (2×d), 128.5 (2×d), 128.1 (2×d), 127.7 (d), 127.6 (2×d), 127.2 (d), 127.0 (2×d), 113.6 (2×d), 109.1 (s), 106.7 (d), 106.1 (s), 101.5 (d), 80.5 (t), 79.0 (d), 75.3 (d), 73.2 (d), 72.8 (t), 71.2 (t), 69.4 (d), 68.9 (t), 68.8 (d), 67.3 (t), 65.8 (t), 57.5 (d), 55.2 (q), 54.9 (q), 53.2 (s), 52.6 (q), 52.0 (q), 48.4 (s), 39.8 (t), 38.8(d), 35.6 (t), 30.3 (t), 25.9 (3×q), 22.4 (q), 18.2 (s), −4.8 (q), −5.1 ppm (q); HRMS: *m*/*z*: calcd for $C_{57}H_{72}O_{16}SiNa$: 1063.4487; found: 1063.4493 [M+Na$^+$], $\Delta =$ 0.5 ppm.

Diol 23α-82b: To a stirred solution of TBS ether 23α-**82a** (25 mg, 0.024 mmol) in CH_2Cl_2 (1 mL) was added pH 7 buffer (0.05 mL) followed by DDQ (8 mg, 0.035 mmol). The reaction was stirred at room temperature for 3 h and then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×5 mL) and then the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash column chromatography (50–100 % ethyl acetate in hexanes) to afford the title compound 23α-**82b** as a colourless oil (20 mg, 91 %). $[\alpha]_D = -16.1$ ($c = 0.13$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.34–7.26 (m, 10H; Ar), 5.56 (s, 1H; H21), 5.05 (brs, 1H; H23), 5.02 (d, $J = 11.8$ Hz, 1H; C*H*HPh), 4.96 (d, $J = 11.5$ Hz, 1H; H18), 4.83 (d, $J =$ 11.2 Hz, 1H; H18), 4.63–4.59 (m, 3H; H15, CH_2Ph), 4.49 (d, $J = 11.9$ Hz, 1H; CH*H*Ph), 4.46 (brs, 1H; H1), 4.15 (d, $J = 14.2$ Hz, 1H; H6), 3.84 (s, 3H; CO_2Me), 3.89–3.70 (m, 4H; 2×H28, H3, H17), 3.60–3.57 (m, 2H; OH, H19), 3.50 (s, 1H; H9), 3.49 (d, $J = 9.2$ Hz, 1H; H19), 3.42 (s, 3H; OMe), 3.39 (s, 3H; CO_2Me), 3.36–3.34 (m, 2H; OH, H19), 2.50 (dd, $J =$ 14.1, 6.1 Hz, 1H; H22), 2.20 (d, $J = 11.5$ Hz, 1H; H2), 2.08–2.05 (m, 2H; H2, H22), 1.87–1.85 (m, 1H; H16), 1.71 (d, $J = 11.2$ Hz, 1H; H16), 1.58 (s, 3H; 30Me), 0.87 (s, 9H; *t*BuSi), 0.08 (s, 3H; SiMe), 0.12 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.6$ (s), 206.3 (s), 174.0 (s), 168.7 (s), 138.1 (s), 137.1 (s), 128.5 (2×d), 128.4 (2×d), 127.7 (d), 127.6 (3×d), 127.3 (2×d), 109.2 (s), 105.9 (s), 101.3 (d), 99.7 (d), 80.7 (t), 78.6 (s), 75.3 (d), 73.0 (d), 72.9 (t), 71.1 (d), 68.9 (t), 68.8 (d), 66.5 (d), 66.0 (t), 65.8 (t), 55.5 (q), 55.2 (d), 53.1 (s), 52.6 (q), 52.0 (q), 52.0 (s), 48.2 (s), 38.2 (d), 35.5 (t), 35.3 (t), 34.0 (t), 25.9 (3×q), 22.6 (q), 18.6 (s), −4.9 (q), −5.0 ppm (q); IR (film): $\nu_{max} = 2927$, 2318, 1721, 1453, 1080, 808 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{49}H_{65}O_{15}Si$: 921.4093; found: 921.4102 [M+H$^+$], $\Delta = 0.9$ ppm.

Diol 23β-82b: To a stirred solution of TBS ether 23β-**82a** (48.1 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) was added pH 7 buffer (1.0 mL) followed by DDQ (0.105 g, 0.46 mmol). The reaction was stirred at room temperature for 3 h and then partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×10 mL) and then the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash column chromatography (50–100 % ethyl acetate in hexanes) to afford the title compound 23β-**82b** as a colourless oil (41 mg, 95 %). $[\alpha]_D = -14.9$ ($c = 2.03$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.29–7.21 (m, 10H; Ar), 5.48 (s, 1H; H21), 5.04 (d, $J = 6.1$ Hz, 1H; H23), 4.97 (d, $J = 11.7$ Hz, 1H; C*H*HPh), 4.92 (d, $J = 11.3$ Hz, 1H; H18), 4.83 (d, $J = 11.2$ Hz, 1H; H18), 4.75 (brs, 1H; H17), 4.59 (app. q, $J = 11.5$ Hz, 2H; CH_2Ar), 4.47–4.44 (m, 2H; CH*H*Ph, H1), 4.33 (m, 1H; H15), 4.15 (d, $J = 14.1$ Hz, 1H; H6), 3.87–3.80 (m, 3H; H3, 2×H28), 3.82 (s, 3H; CO_2Me), 3.56 (d, $J = 9.3$ Hz, 1H; H19), 3.51 (s, 1H; H9), 3.49 (d, $J =$ 9.4 Hz, 1H; H19), 3.46 (s, 3H; OMe), 3.41 (d, $J = 4.8$ Hz, 1H; OH), 3.40–3.34 (m, 2H; H5, OH), 3.39 (s, 3H; CO_2Me), 2.43 (dd, $J = 9.0$, 1.6 Hz, 1H; H22), 2.38 (d, $J = 10.1$ Hz, 1H; H22), 2.23 (m, 1H; H2), 2.14 (d, $J =$ 15.8 Hz, 1H; H2), 1.78 (m, 2H; 2×H16), 1.63 (s, 3H; 30Me), 0.90 (s, 9H; *t*BuSi), 0.12 (s, 3H; SiMe), 0.07 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.5$ (s), 206.3 (s), 174.1 (s), 168.1 (s), 138.2 (s), 137.1 (s), 128.5 (2×d), 128.4 (2×d), 127.7 (d), 127.7 (d), 127.6 (2×d), 127.2 (2×d), 109.2 (s), 106.0 (s), 103.2 (d), 102.1 (d), 80.7 (t), 78.4 (s), 75.3 (d), 73.0 (d), 72.8 (t), 70.7 (d), 68.9 (t), 68.7 (d), 66.6 (d), 66.5 (t), 65.8 (t), 57.3 (d), 56.3 (s), 55.1 (q), 53.2 (s), 52.7 (q), 52.0 (q), 48.4 (s), 38.2 (d), 36.5 (t), 35.6 (t), 34.2 (t), 25.9 (3×q), 22.3 (q), 18.2 (s), −5.0 (q), −5.1 ppm (q); IR (film): $\nu_{max} = 2955$, 2930, 2860, 1750, 1720, 1460, 1440, 1240, 1070, 840 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{63}H_{86}O_{16}Si_2Na$: 943.3906; found: 943.3907 [M+Na$^+$], $\Delta = 0.1$ ppm.

Xanthate ester 23α-87: A solution of diol 23α-**82b** (45 mg, 0.049 mmol) in THF (6 mL) was cooled to −78 °C and then carbon disulfide (0.015 mL, 0.25 mmol) was added. After 30 min NaHMDS (2.0 M in THF, 0.028 mL, 0.055 mmol) was added and after a further 30 min methyl iodide (0.028 g, 0.055 mmol) was added. The reaction was stirred at −78 °C for 1 h before quenching with saturated aqueous NH_4Cl solution (0.1 mL). The reaction was then partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL), the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (20–50 % ethyl acetate in hexanes) afforded title compound 23α-**87** as a yellow oil (43 mg, 86 %). $[\alpha]_D = -9.4$ ($c = 0.09$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.34$–7.24 (m, 10H; Ar), 6.06 (dd, $J =$ 9.3, 4.7 Hz, 1H; H17), 5.46 (brs, 1H; H21), 5.19 (brs, 1H; H23), 5.00 (d, $J = 11.8$ Hz, 1H; C*H*HPh), 4.96 (d, J = 11.3 Hz, 1H; H18), 4.83 (d, $J =$ 11.2 Hz, 1H; H18), 4.75–4.73 (m, 1H; H15), 4.69 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.56 (d, $J = 11.6$ Hz, 1H; CH*H*Ph), 4.48 (d, $J = 11.8$ Hz, 1H; CH*H*Ph), 4.44 (brs, 1H; H1), 4.13 (d, $J = 14.2$ Hz, 1H; H6), 3.88–3.82 (m, 2H; H3, H28), 3.85 (s, 3H; CO_2Me), 3.78 (d, $J = 7.9$ Hz, 1H; H28), 3.53–3.47 (m, 2H; H9, H19), 3.43 (m, 4H; H19, CO_2Me), 3.39 (s, 3H; OMe), 3.36 (d, $J = 14.3$ Hz, 1H; H5), 3.24 (brs, 1H; OH), 2.55 (s, 3H; SMe), 2.46 (dd, $J = 14.0$, 6.0 Hz, 1H; H22), 2.25–2.10 (m, 4H; H22, H2, H16), 1.88 (d, $J = 13.0$ Hz, 1H; H16), 1.57 (s, 3H; 30Me), 0.88 (s, 9H; *t*BuSi), 0.09 (s, 3H; SiMe), 0.04 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.5$ (s), 206.5 (s), 206.4 (s), 174.0 (s), 168.8 (s), 138.5 (s), 137.1 (s), 128.5 (2×d), 128.2 (4×d), 127.7 (d), 127.7 (2×d), 127.4 (d), 108.9 (s), 105.9 (s), 104.1 (d), 102.0 (d), 81.2 (t), 79.2 (s), 75.2 (d), 72.8 (d), 72.8 (t), 68.9 (d), 68.6 (t), 68.0 (t), 65.8 (d), 65.7 (t), 63.9 (d), 56.5 (d), 55.7 (q), 53.4 (s), 53.1 (s), 52.7 (q), 52.0 (q), 48.2 (s), 38.1 (d), 36.7 (t), 35.6 (t), 30.5 (t), 25.9 (3×q), 22.6 (q), 19.1 (q), 18.2 (s), −4.9 (q), −5.1 ppm (q); HRMS: *m*/*z*: calcd for $C_{51}H_{66}O_{15}S_2SiNa$: 1033.3510; found: 1033.3549 [M+Na$^+$], $\Delta = 3.8$ ppm.

Xanthate ester 23β-87: A solution of diol 23β-**82b** (46 mg, 0.05 mmol) in THF (5 mL) was cooled to −78 °C and then carbon disulfide (0.015 mL, 0.25 mmol) added. After 30 min NaHMDS (2.0 M in THF, 0.028 mL, 0.055 mmol) was added and after a further 30 min methyl iodide (0.028 g, 0.055 mmol) was added. The reaction was stirred at −78 °C for 1 h before quenching with saturated aqueous NH_4Cl solution (0.1 mL). The reaction was then partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL), the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (20–50 % ethyl acetate in hexanes) afforded starting diol 23β-**82b** (11 mg, 24 %) followed by the title compound 23β-**87** as a highly unstable yellow oil (29 mg, 57 %) which was used immediately in the subsequent step.

(23*R*)-3-*O*-*tert*-Butyldimethylsilyl-13,14-desepoxy-1-detigloyl-11,20-*O*,*O*-dibenzyl-22,23-dihydro-23-methoxy-7-oxo-azadirachtin (23α-91): To a solution of xanthate 23α-**87** (24 mg, 0.024 mmol) in toluene (0.82 mL) was added AIBN (0.4 mg, 0.0024 mmol). The reaction vessel was then heated to 110 °C and a syringe pump used to introduce a solution of AIBN (1.5 mg, 0.096 mmol) and tributyltin hydride (19.3 μL, 0.072 mmol) in toluene (5.2 mL) over 2 h. The reaction was heated for a further 12 h before cooling to room temperature and partitioning between acetonitrile

(20 mL) and hexane (20 mL). The acetonitrile layer was then separated and concentrated in vacuo. Column chromatography (10–40% ethyl acetate in hexanes) afforded the title compound 23α-**91** as a colourless oil (19 mg, 90%). $[\alpha]_D = -11.2$ ($c = 0.47$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.36$–7.20 (m, 10H; Ar), 5.40 (dd, $J = 6.3$, 3.8 Hz, 1H; H23), 5.24 (brs, 1H; H21), 5.01 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.70 (brs, 1H; H15), 4.59 (d, $J = 11.4$ Hz, 1H; C*H*HPh), 4.52 (d, $J = 11.4$ Hz, 1H; CH*H*Ph), 4.46 (d, $J = 11.6$ Hz, 1H; CH*H*Ph), 4.43 (brs, 1H; H1), 4.24 (d, $J = 14.3$ Hz, 1H; H6), 3.87 (d, $J = 8.1$ Hz, 1H; H28), 3.80 (s, 3H; OMe), 3.78 (d, $J = 8.1$ Hz, 1H; H28), 3.56 (d, $J = 9.3$ Hz, 1H; H19), 3.54 (s, 1H; H9), 3.49 (d, $J = 9.3$ Hz, 1H; H19), 3.48 (s, 3H; OMe), 3.42 (s, 3H; OMe), 3.18 (d, $J = 9.8$ Hz, 1H; H28), 3.12 (d, $J = 14.3$ Hz, 1H; H5), 2.77 (d, $J = 6.0$ Hz, 1H; H17), 2.38 (dd, $J = 15.0$, 6.5 Hz, 1H; H22), 2.18–2.28 (m, 2H; H2, H22), 2.12 (app. d, $J = 15.0$ Hz, 1H; H2), 1.91–1.89 (m, 1H; H16), 1.77 (s, 3H; 18Me), 1.70 (d, $J = 11.3$ Hz, 1H; H16), 1.56 (s, 3H; 30Me), 0.88 (s, 9H; *t*BuSi), 0.10 (s, 3H; SiMe), 0.02 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 209.1$ (s), 173.8 (s), 168.7 (s), 140.7 (s), 138.5 (s), 137.7 (s), 137.0 (s), 128.5 (2×d), 128.3 (2×d), 127.8 (d), 127.7 (2×d), 127.5 (2×d), 127.2 (d), 107.9 (d), 106.0 (s), 103.4 (d), 86.0 (s), 80.6 (d), 75.6 (d), 72.8 (d), 72.5 (t), 68.7 (t), 68.6 (d), 65.7 (t), 65.2 (t), 57.9 (q), 56.6 (s), 53.6 (q), 53.4 (q), 53.1 (d), 53.0 (s), 52.1 (d), 47.8 (s), 38.8 (t), 38.4 (d), 38.2 (t), 35.5 (t), 25.8 (3×q), 20.4 (q), 18.0 (s), 17.4 (q), −5.1 (q), −5.3 ppm (q); IR (film): $\nu_{max} = 3521$, 2927, 1754, 1724, 1454, 1243, 1062, 840 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{49}H_{64}O_{15}SiNa$: 927.3963; found: 927.3980 [M+Na$^+$], $\Delta = 1.8$ ppm.

(23*S*)-3-*O*-*tert*-Butyldimethylsilyl-13,14-desepoxy-1-detigloyl-11,20-*O*,*O*-dibenzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (23β-91): To a solution of xanthate 23β-**87** (10 mg, 0.010 mmol) in toluene (0.5 mL) was added AIBN (0.16 mg, 0.001 mmol). The reaction vessel was then heated to 110°C and a syringe pump used to introduce a solution of AIBN (0.63 mg, 0.004 mmol) and tributyltin hydride (0.008 mL, 0.030 mmol) in toluene (2.1 mL) over 2 h. The reaction was heated for a further 12 h before cooling to room temperature and partitioning between acetonitrile (10 mL) and hexane (10 mL). The acetonitrile layer was then separated and concentrated in vacuo. Column chromatography (20–50% ethyl acetate in hexanes) afforded the title compound 23β-**91** as a colourless oil (8.2 mg, 91%). $[\alpha]_D = +8.2$ ($c = 0.15$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.36$–7.20 (m, 10H; Ar), 5.30 (dd, $J = 6.2$, 4.2 Hz, 1H; H23), 5.10 (br.s, 1H; H21), 4.98 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.80 (brs, 1H; H15), 4.50 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.44 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.43 (brs, 1H; H1), 4.38 (d, $J = 11.6$ Hz, 1H; CH*H*Ph), 4.22 (d, $J = 14.3$ Hz, 1H; H6), 3.84 (d, $J = 4.6$ Hz, 1H; H28), 3.82–3.77 (m, 2H; H3, H28), 3.80 (s, 3H; CO_2Me), 3.55 (d, $J = 9.3$ Hz, 1H; H19), 3.52 (s, 1H; H9), 3.48 (d, $J = 9.3$ Hz, 1H; H19), 3.42 (s, 3H; CO_2Me), 3.41 (s, 3H; OMe), 3.10 (d, $J = 14.3$ Hz, 1H; H5), 2.77 (d, $J = 5.2$ Hz, 1H; H17), 2.48 (dd, $J = 15.4$, 6.2 Hz, 1H; H22), 2.20 (app. d, $J = 15.8$ Hz, 1H; H2), 2.15 (dd, $J = 15.4$, 4.2 Hz, 1H; H22), 2.10 (app. d, $J = 15.8$ Hz, 1H; H2), 1.92 (d, $J = 11.1$ Hz, 1H; H16), 1.82 (ddd, $J = 11.1$, 5.2, 4.7 Hz, 1H; H16), 1.77 (s, 3H; 18Me), 1.51 (s, 3H; 30Me), 0.88 (s, 9H; *t*BuSi), 0.12 (s, 3H; SiMe), −0.01 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 209.1$ (s), 173.8 (s), 171.1 (s), 140.7 (s), 138.3 (s), 137.7 (s), 137.0 (s), 128.5 (2×d), 128.3 (2×d), 127.8 (d), 127.7 (2×d), 127.3 (d), 126.9 (2×d), 108.9 (d), 106.0 (s), 104.3 (d), 87.1 (s), 81.4 (d), 75.6 (d), 72.8 (d), 72.5 (t), 68.7 (t), 68.5 (d), 65.7 (t), 64.8 (t), 58.0 (d), 56.4 (q), 53.7 (s), 53.2 (q), 53.1 (s), 52.8 (d), 52.1 (q), 47.8 (s), 39.1 (t), 38.4 (d), 38.3 (t), 35.5 (t), 25.8 (3×q), 20.4 (q), 18.0 (s), 17.4 (q), −5.1 (q), −5.3 ppm (q); IR (film): $\nu_{max} =$ 2950, 1725, 1453, 142, 1092, 841 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{49}H_{64}O_{15}SiNa$: 927.3963; found: 927.3931 [M+Na$^+$], $\Delta = 3.5$ ppm.

(23*S*)-3-*O*-*tert*-Butyldimethylsilyl-1-detigloyl-11,20-*O*,*O*-dibenzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (92): To a solution of alkene 23α-**91** (9 mg, 0.010 mmol) in MeOH (1 mL) was added $NaHCO_3$ (0.017 g, 0.20 mmol), MMPP.6H_2O (0.10 g, 0.20 mmol), and 5-*tert*-butyl-4-hydroxy-2-methylphenylsulfide (0.071 g, 0.20 mmol). The reaction vessel was sealed and heated to 110°C for 7 d. After cooling to room temperature the reaction was partitioned between saturated aqueous $Na_2S_2O_3$ solution (5 mL) and ethyl acetate (5 mL), the organic layer was separated and further washed with saturated aqueous $NaHCO_3$ solution (5 mL), then dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (10–50% ethyl acetate in hexanes) afforded the title compound **92** as a colourless oil (2 mg, 22%) followed by starting alkene 23α-**91** (6 mg, 67%). $[\alpha]_D = +5.8$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.36$–7.20 (m, 10H; Ph), 5.41 (s, 1H; H21), 5.22 (dd, $J = 6.4$, 2.8 Hz, 1H; H23), 5.12 (s, 1H; H15), 4.96 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.45 (d, $J = 12.2$ Hz, 1H; CH*H*Ph), 4.42 (d, $J = 12.2$ Hz, 1H; C*H*HPh), 4.40 (d, $J = 11.6$ Hz, 1H; C*H*HPh), 4.38–4.37 (m, 1H; H1), 4.15 (d, $J = 14.1$ Hz, 1H; H6), 4.08 (d, $J = 14.1$ Hz, 1H; H5), 3.89–3.88 (m, 1H; H28), 3.87–3.79 (m, 3H; H28, H3, H9), 3.82 (s, 3H; OMe), 3.58 (d, $J = 9.4$ Hz, 1H; H19), 3.50 (d, $J = 9.4$ Hz, 1H; H19), 3.42 (s, 3H; OMe), 3.37 (s, 3H; OMe), 2.55 (d, $J = 5.8$ Hz, 1H; H17), 2.50 (dd, $J = 6.4$, 5.3 Hz, 1H; H22), 2.22 (dt, $J = 13.0$, 2.5 Hz, 1H; H2), 2.15–2.08 (m, 2H; H2, H22), 1.78 (s, 3H; 18Me), 1.65 (d, $J = 12.6$ Hz, 1H; H16), 1.50 (s, 3H; 30Me), 1.49 (ddd, $J = 12.6$, 5.9, 3.0 Hz, 1H; H16), 0.90 (s, 9H; *t*BuSi), 0.12 (s, 3H; SiMe), −0.02 ppm (s, 3H; SiMe); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.3$ (s), 174.4 (s), 168.6 (s), 138.1 (s), 136.9 (s), 128.5 (2×d), 128.4 (2×d), 127.8 (2×d), 127.7 (d), 127.4 (2×d), 126.8 (d), 107.7 (s), 105.8 (d), 103.9 (d), 86.7 (s), 78.2 (d), 75.3 (d), 73.9 (d), 72.9 (t), 68.9 (t), 68.3 (s), 68.1 (d), 66.9 (s), 65.7 (t), 64.4 (t), 59.8 (q), 55.5 (q), 53.3 (s), 53.0 (q), 52.6 (s), 51.9 (d), 48.5 (s), 47.0 (d), 41.0 (t), 37.3 (d), 35.8 (t), 25.5 (3×q), 25.2 (t), 19.6 (q), 17.9 (s), 16.5 (q), −5.1 (q), −5.8 ppm (q); IR (film): $\nu_{max} =$ 3521, 2931, 1756, 1723, 1454, 1241, 1066 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{49}H_{64}O_{15}SiNa$: 943.3912; found: 943.3947 [M+Na$^+$], $\Delta = 3.7$ ppm.

(23*S*)-3-*O*-*tert*-Butyldimethylsilyl-1-detigloyl-11,20-*O*,*O*-dibenzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (92): To a solution of alkene 23β-**91** (8 mg, 0.009 mmol) in MeOH (2 mL) was added $NaHCO_3$ (0.015 g, 0.18 mmol), MMPP.6H_2O (89 mg, 0.18 mmol) and 5-*tert*-butyl-4-hydroxy-2-methyl phenylsulfide (0.064 g, 0.18 mmol). The reaction vessel was sealed and heated to 110°C for 7 d. After cooling to room temperature the reaction was partitioned between saturated aqueous $Na_2S_2O_3$ solution (5 mL) and ethyl acetate, the organic layer was separated and further washed with saturated aqueous $NaHCO_3$ solution (5 mL), then dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (20–50% ethyl acetate in hexanes afforded the title compound **92** as a colourless oil (5.4 mg, 65%) followed by starting alkene 23β-**91** (2.5 mg, 30%).

(23*S*)-3-desacetyl-1-detigloyl-11,20-bis-*O*-benzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (92a): To a stirred solution of silyl ether **92** (1.1 g, 1.2 mmol) in THF (20 mL) was added TBAF (1.0 M in THF, 1.8 mL, 1.8 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo and purified by flash colmn chromatography (50–100% ethyl acetate in hexane) to afford the diol **92a** (921 mg, 95%) as a colourless oil. $[\alpha]_D = +11.8$ ($c = 0.10$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.36$–7.23 (m, 10H; Ar), 5.50 (s, 1H; H21), 5.23 (dd, $J = 6.4$, 2.6 Hz, 1H; H23), 5.08 (brs, 1H; H15), 4.99 (d, $J = 12.0$ Hz, 1H; H19), 4.51 (d, $J = 12.6$ Hz, 1H; C*H*HPh), 4.49–4.47 (m, 2H; H19, H1), 4.43 (d, $J = 12.5$ Hz, 1H; CH*H*Ph), 4.21 (d, $J = 14.0$ Hz, 1H; H6), 4.04 (d, $J = 8.2$ Hz, 1H; H28), 3.95 (m, 2H; H28, H3), 3.88 (d, $J = 14.4$ Hz, 1H; H5), 3.84 (m, 5H; CO_2Me, H9, H17), 3.76 (d, $J = 9.6$ Hz, 1H; C*H*HPh), 3.54 (d, $J = 9.6$ Hz, 1H; C*H*HPh), 3.47 (s, 3H; CO_2Me), 3.39 (s, 3H; OMe), 2.78 (d, $J = 6.3$ Hz, 1H; OH), 2.64 (d, $J = 5.8$ Hz, 1H; OH), 2.49 (d, $J = 15.1$ Hz, 1H; H22), 2.24 (m, 2H; H2), 2.12 (dd, $J = 15.1$, 6.5 Hz, 1H; H22), 1.82 (s, 3H; 18Me), 1.64 (d, $J = 12.6$ Hz, 1H; H16), 1.57 (s, 3H; 30Me), 1.52 ppm (m, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.2$ (s), 174.2 (s), 169.0 (s), 138.1 (s), 136.9 (s), 128.5 (2×d), 128.4 (2×d), 127.8 (d), 127.7 (2×d), 127.4 (d), 126.9 (2×d), 107.7 (d), 105.8 (s), 103.9 (d), 86.9 (s), 78.0 (d), 75.3 (d), 73.6 (d), 72.9 (t), 69.3 (t), 68.3 (s), 67.4 (d), 67.0 (s), 65.9 (t), 64.4 (t), 55.5 (q), 53.5 (s), 53.0 (q), 52.7 (s), 51.9 (q), 48.7 (s), 46.9 (d), 41.3 (t), 37.7 (d), 35.6 (d), 35.5 (t), 25.1 (t), 20.0 (q), 16.5 ppm (q); IR (film): $\nu_{max} =$ 3456, 2953, 1753, 1725, 1440, 1286, 1092 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{43}H_{50}O_{15}Na$: 829.3047; found: 829.3040 [M+Na$^+$], $\Delta = 0.9$ ppm.

(23*S*)-3-Desacetyl-1-detigloyl-11-*O*-benzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (95): To a stirred solution of bis-benzyl ether **92a** (16 mg, 0.022 mmol) in ethanol (3 mL) was added Pd/C (30 wt%, cat.), and the resulting solution saturated with H_2 gas. After 3 h the reaction was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by flash column chromatography (70–90% ethyl acetate in petrol) to afford triol **95** (15.2 mg, 95%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.30 (m, 2H; Ph), 7.28–7.26 (m,

3H; Ph), 5.23 (s, 1H; H21), 5.14 (dd, J=3.8, 2.4 Hz, 1H; H23), 4.95 (d, J=11.6 Hz, 1H; H19), 4.77 (d, J=14.4 Hz, 1H; H6), 4.65 (d, J=11.6 Hz, 1H; H19), 4.46 (m, 1H; H1), 4.41 (t, J=3.6 Hz, 1H; H3), 4.28 (d, J=9.9 Hz, 1H; C*H*HPh), 4.14 (d, J=8.5 Hz, 1H; H28), 4.11 (d, J=8.5 Hz, 1H; H28), 3.79 (s, 3H; CO_2Me), 3.77 (m, 1H; H15), 3.74 (s, 1H; H9), 3.70 (brs, 1H; OH), 3.64 (s, 3H; CO_2Me), 3.61 (d, J=9.9 Hz, 1H; CH*H*Ph), 3.38 (s, 3H; 23OMe), 3.33 (d, J=7.3 Hz, 1H; OH), 3.20 (d, J=14.4 Hz, 1H; H5), 2.91 (s, 1H; OH), 2.42 (d, J=5.4 Hz, 1H; H17), 2.32 (dd, J=14.6, 6.3 Hz, 1H; H22), 2.25 (dt, J=15.8, 2.9 Hz, 1H; H2), 2.17 (dd, J=14.6, 3.8 Hz, 1H; H22), 2.01 (dt J=17.5 Hz, t not resolved, 1H; H2), 1.85 (s, 3H; 30Me), 1.72 (d, J=12.8 Hz, 1H; H16), 1.62 (s, 3H; 18Me), 1.52 ppm (m, 1H; H16); ^{13}C NMR (150 MHz, $CDCl_3$): δ=206.1 (s), 173.8 (s), 170.5 (s), 137.0 (s), 128.5 (2×d), 127.9 (d), 127.6 (2×d), 106.4 (d), 105.8 (s), 105.6 (d), 80.9 (s), 77.0 (d), 75.9 (d), 73.3 (t), 72.1 (d), 70.7 (t), 67.4 (s), 67.1 (d), 66.5 (t), 66.0 (s), 56.2 (d), 55.9 (q), 54.7 (s), 53.1 (q), 52.8 (s), 52.2 (q), 50.0 (s), 48.9 (d), 48.3 (t), 39.9 (d), 34.0 (t), 24.6 (t), 20.4 (q), 17.2 ppm (q); IR (film): ν_{max} = 3403, 2930, 1725, 1449, 1241, 1062 cm^{-1}; HRMS: m/z: calcd for $C_{36}H_{45}O_{15}Na$: 739.2637; found: 739.2601 [M+Na$^+$], Δ=3.2 ppm.

(23*S*)-11-Benzyloxy-1-detigloyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin (95a): Acetic anhydride (0.27 mL, 0.3 mmol), NEt_3 (0.66 mL, 0.5 mmol), DMAP (10 mg) and triol **95** (0.34 g, 0.5 mmol) were stirred in CH_2Cl_2 (70 mL) for 4 h at room temperature. The reaction was washed with water (50 mL), then the organic layer was separated and extracted further with CH_2Cl_2 (3×50 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (90% ethyl acetate in petrol) afforded **95a** (0.29 g, 76%) as a colourless, glassy solid. M.p. 89–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.26 (m, 2H; Ph), 7.25–7.23 (m, 3H; Ph), 5.53 (app. t, J=2.8 Hz, 1H; H3), 5.27–5.24 (m, 2H; H21, H23), 5.01 (d, J=2.1 Hz, 1H; H1), 4.97 (d, J=11.5 Hz, 1H; H19), 4.48 (d, J=11.5 Hz, 1H; H19), 4.23 (d, J=13.9 Hz, 1H; C*H*HPh), 3.95 (d, J=8.6 Hz, 1H; H28), 3.89–3.83 (m, 5H; H6, CO_2Me, CH*H*Ph), 3.72 (m, 1H; H15), 3.70 (brs, 1H; OH), 3.55 (d, J=8.6 Hz, 1H; H28), 3.51 (s, 3H; CO_2Me), 3.40 (m, 5H; H9, OMe, OH), 3.03 (d, J=10.8 Hz, 1H; H5), 2.43 (d, J=5.7 Hz, 1H; H17), 2.38 (app. dt, J=16.3, 3.1 Hz, 1H; H2), 2.32 (dd, J=14.9, 3.1 Hz, 1H; H22), 2.28–2.20 (m, 2H; H2, H22), 2.07 (s, 3H; 18Me), 1.82 (s, 3H; OAc), 1.69 (m, 1H; H16), 1.44 (dd, J=12.8, 3.2 Hz, 1H; H16), 1.58 ppm (s, 3H; 30Me); ^{13}C NMR (150 MHz, $CDCl_3$): δ=205.6 (s), 173.1 (s), 169.1 (s), 168.8 (s), 136.3 (s), 128.5 (2×d), 127.9 (d), 127.8 (2×d), 107.1 (d), 105.8 (s), 105.6 (d), 81.2 (s), 77.9 (d), 75.3 (d), 73.1 (t), 72.6 (d), 69.2 (t), 68.5 (d), 68.2 (s), 67.3 (s), 66.0 (t), 58.9 (d), 55.7 (q), 53.1 (q), 52.6 (s), 52.3 (q), 51.9 (s), 49.1 (d), 48.4 (s), 48.3 (t), 39.1 (d), 33.7 (t), 25.4 (t), 20.8 (q), 16.9 (q), 14.2 ppm (q); HRMS: m/z: calcd for $C_{38}H_{47}O_{16}$: 759.2864; found: 759.2898 [M+H$^+$], Δ=4.5 ppm.

(23*S*)-11-*O*-Benzyl-22,23-dihydro-23-methoxy-7-oxoazadirachtin 95b: To a stirred solution of diol **95a** (15 mg, 0.020 mmol) in toluene (0.5 mL) was added Cs_2CO_3 (129 mg, 0.40 mmol) followed by a mixed anhydride from tiglic acid and the Yamaguchi acid chloride (122 mg, 0.40 mmol). The resulting mixture was heated in a sealed tube for 6 d before cooling to room temperature and partitioning between ethyl acetate (5 mL) and water (5 mL). The organic layer was separated, dried ($MgSO_4$) and the solvent removed in vacuo. Flash colum chromatography (70% ethyl acetate in hexanes) provided tiglate ester **95b** (8.5 mg, 50%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.27 (m, 5H; Ar), 6.61 (q, J=7.1 Hz, 1H; H3′), 5.50 (app. t, J=2.8 Hz, H3), 5.44 (d, J=14.4 Hz, 1H; H6), 5.22 (s, 1H; H21), 5.07 (dd, J=6.1, 1.8 Hz, 1H; H23), 4.80 (app. t, J=2.7 Hz, 1H; H1), 4.68 (d, J=10.7 Hz, 1H; H19), 4.54 (d, J=9.9 Hz, 1H; H28), 4.40 (d, J=10.7 Hz, 1H; H19), 4.10 (d, J=9.1 Hz, 1H; C*H*HPh), 3.86 (d, J=3.3 Hz, 1H; H15), 3.84 (s, 3H; CO_2Me), 3.79–3.77 (m, 2H; H28, CH*H*Ph), 3.70 (s, 1H; H9), 3.68 (s, 3H; CO_2Me), 3.59 (s, 1H; OH), 3.38 (s, 3H; OMe), 2.76 (d, J=14.4 Hz, 1H; H5), 2.43–2.41 (m, 2H; H17, H22), 2.33 (app. dt, J=16.9, 2.5 Hz, 1H; H2), 2.21 (app. dt, J=16.9, 3.2 Hz, 1H; H2), 2.06 (dd, J=14.3, 4.5 Hz, 1H; H22), 1.94 (s, 3H; 18Me), 1.90 (s, 3H; OAc), 1.80 (s, 3H; 5′Me), 1.76 (d, J=12.7 Hz, 1H; H16), 1.17 (dd, J=7.1, 0.9 Hz, 3H; 4′Me), 1.58 (s, 3H; 30Me), 1.52 ppm (m, 1H; H16); ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.0 (s), 172.6 (s), 169.9 (s), 169.6 (s), 166.4 (s), 137.8 (d), 136.8 (s), 129.0 (s), 128.7 (2×d), 128.5 (3×d), 107.5 (d), 107.3 (s), 105.0 (d), 81.1 (s), 76.8 (d), 76.4 (d), 73.5 (t), 70.5 (d), 70.1 (t), 67.9 (t), 67.0 (s), 66.7 (d), 65.5 (s), 56.5 (q), 53.9 (s), 53.7 (d), 53.6 (s), 53.5 (q), 53.5 (q), 48.9 (d), 48.8 (t), 48.6 (s), 46.3 (d), 30.2 (t), 24.7 (t), 22.0 (q), 21.2 (q), 18.7 (q), 14.5 (q), 12.5 ppm (q); HRMS: m/z: calcd for $C_{43}H_{53}O_{17}$: 841.3283; found: 841.3311 [M+H$^+$], Δ=3.3 ppm.

(23*S*)-22,23-Dihydro-23-methoxyazadirachtin 97 (vepaol): Vepaol was prepared from **95b** following the previously reported steps.[86]

Azadirachtin 1: To a stirred solution of vepaol **97** (50 mg, 0.066 mmol) in 1,2-dichloroethane (2.5 mL) was added benzeneselenol (150 μL, 1.33 mmol) followed by PPTS (cat., five crystals). The resulting mixture was heated at reflux for 4 h, then loaded directly onto silica and purified by flash column chromatography (20 to 50% ethyl acetate in hexane) to afford selenide **98** (59 mg, quantitative) as a highly unstable yellow oil. Selenide **98** (59 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Pyridine (27 μL, 0.33 mmol) followed by hydrogen peroxide (30% aq., 37 μL, 0.33 mmol) was then added and the resulting mixture stirred for 10 min. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution. (1 mL) and the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (80% ethyl acetate in hexane) afforded azadirachtin **6** (41 mg, 85% over 2 steps) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.92 (q, J=7.1 Hz, 1H; H3′), 6.46 (d, J=2.9 Hz, 1H; H23), 5.64 (s, 1H; H21), 5.50 (app. t, J=2.8 Hz, 1H; H3), 5.05 (d, J=2.8 Hz, 1H; H22), 5.02 (s, 1H; OH), 4.76 (app. t, J=2.8 Hz, 1H; H1), 4.74 (brs, 1H; H7), 4.67 (d, J=3.5 Hz, 1H; H15), 4.61 (dd, J=12.5, 2.7 Hz, 1H; H6), 4.15 (d, J=9.7 Hz, 1H; H19), 4.07 (d, J=9.0 Hz, 1H; H28), 3.79 (s, 3H; CO_2Me), 3.77 (d, J=9.0 Hz, 1H; H28), 3.69 (s, 3H; CO_2Me), 3.63 (d, J=9.7 Hz, 1H; H19), 3.35 (d, J=12.4 Hz, 1H; H5), 3.34 (s, 1H; H9), 2.84 (brs, 1H; OH), 2.79 (brs, 1H; OH), 2.38 (d, J=5.3 Hz, 1H; H17), 2.34 (app. dt, J=16.9 Hz, t not resolved, 1H; H2), 2.23 (app. dt, J=16.9, 3.3 Hz, 1H; H2), 2.00 (s, 3H; 18Me), 1.95 (s, 3H; OAc), 1.85 (s, 3H; 5′Me), 1.78 (d, J=7.1 Hz, 3H; 4′Me), 1.75 (s, 3H; 30Me), 1.76 (ddd, J=13.2, 5.3, 3.5 Hz, 1H; H16), 1.31 ppm (ddd, J=13.2, 0.4, 0.3 Hz, 1H; H16); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.4 (s), 171.8 (s), 169.7 (s), 166.2 (s), 146.9 (d), 137.8 (d), 128.5 (s), 108.6 (d), 107.5 (d), 104.2 (s), 83.5 (s), 76.4 (d), 74.3 (d), 73.9 (d), 73.1 (t), 70.5 (d), 70.0 (s), 68.0 (t), 67.5 (s), 66.9 (d), 53.2 (q), 52.7 (q), 52.5 (s), 50.2 (s), 48.6 (d), 45.5 (s), 44.7 (d), 36.9 (d), 29.7 (t), 25.0 (t), 21.3 (q), 20.8 (q), 18.4 (q), 14.3 (q), 11.9 ppm (q), IR (film): ν_{max} = 3441, 2923, 1741, 1438, 1376, 1265 cm^{-1}.

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[1] J. H. Butterworth, E. D. Morgan, *Chem. Commun.* **1968**, 23–24.
[2] W. M. Blaney, M. S. J. Simmonds, S. V. Ley, J. C. Anderson, P. L. Toogood, *Entomol. Exp. Appl.* **1990**, *55*, 149–160.
[3] M. S. J. Simmonds, W. M. Blaney, S. V. Ley, J. C. Anderson, P. L. Toogood, *Entomol. Exp. Appl.* **1990**, *55*, 169–181.
[4] M. S. J. Simmonds, W. M. Blaney, R. B. Grossman, S. V. Ley, *J. Insect Physiol.* **1995**, *41*, 555–564.
[5] M. S. J. Simmonds, W. M. Blaney, S. V. Ley, J. C. Anderson, R. Bänteli, A. A. Denholm, P. C. W. Green, R. B. Grossman, C. Gutteridge, L. Jennens, S. C. Smith, P. L. Toogood, A. Wood, *Entomol. Exp. Appl.* **1995**, *77*, 69–80.
[6] A. J. Nisbet, A. J. Mordue, L. M. Williams, L. Hannah, L. Jennens, S. V. Ley, W. Mordue, *Tissue Cell* **1996**, *28*, 725–729.
[7] A. J. Mordue Luntz, A. J. Nisbet, L. Jennens, S. V. Ley, W. Mordue, *A. Juss. Int. Neem Conference*, Gatton (Australia), **1996**, Chapter 22.

[8] A. J. Nisbet, A. J. Mordue Luntz, R. B. Grossman, L. Jennens, S. V. Ley, W. Mordue, *Arch. Insect Biochem. Physiol.* **1997**, *34*, 461–473.
[9] A. J. Mordue Luntz, M. S. J. Simmonds, S. V. Ley, W. M. Blaney, W. Mordue, M. Nasiruddin, A. J. Nisbet, *Pestic. Sci.* **1998**, 277–284.
[10] A. Salehzadeh, A. Jabbar, L. Jennens, S. V. Ley, R. S. Annadurai, R. Adams, R. H. C. Strang, *Pest. Manag. Sci.* **2002**, *58*, 268–276.
[11] S. L. Robertson, W. Ni, T. S. Dhadialla, A. J. Nisbet, C. McCusker, S. V. Ley, W. Mordue, A. J. Mordue-Luntz, *Arch. Insect Biochem. Physiol.* **2007**, *64*, 200–208.
[12] A. J. Mordue, A. Blackwell, *J. Insect Physiol.* **1993**, *39*, 903–924.
[13] H. B. Broughton, S. V. Ley, A. M. Z. Slawin, D. J. Williams, E. D. Morgan, *J. Chem. Soc. Chem. Commun.* **1986**, 46–47.
[14] J. N. Bilton, H. B. Broughton, P. S. Jones, S. V. Ley, Z. Lidert, E. D. Morgan, H. S. Rzepa, R. N. Sheppard, A. M. Z. Slawin, D. J. Williams, *Tetrahedron* **1987**, *43*, 2805–2815.
[15] W. Kraus, M. Bokel, A. Klenk, H. Poehnl, *Tetrahedron Lett.* **1985**, *26*, 6435–6438.
[16] C. J. Turner, M. S. Tempesta, R. B. Taylor, M. G. Zagorski, J. S. Termini, D. R. Schroeder, K. Nakanishi, *Tetrahedron* **1987**, *43*, 2789–2803.
[17] W. Kraus, M. Bokel, A. Bruhn, R. Cramer, I. Klaiber, A. Klenk, G. Nagl, H. Poehnl, H. Sadlo, B. Volger, *Tetrahedron* **1987**, *43*, 2817–2830.
[18] T. R. Govindachari, G. Gopalakrishnan, R. Raghunathan, S. S. Rajan, *Curr. Sci.* **1994**, *66*, 295–297.
[19] S. V. Ley, N. S. Simpkins, A. J. Whittle, *J. Chem. Soc. Chem. Commun.* **1983**, 503–505.
[20] D. M. Hollinshead, S. C. Howell, S. V. Ley, M. Mahon, N. M. Ratcliffe, P. A. Worthington, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1579–1589.
[21] A. T. Merritt, S. V. Ley, *Nat. Prod. Rep.* **1992**, *9*, 243–287.
[22] S. V. Ley, D. Santafianos, W. M. Blaney, M. S. J. Simmonds, *Tetrahedron Lett.* **1987**, *28*, 221–224.
[23] Y. Nishikimi, T. Iimori, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 3354–3359.
[24] J. Jauch, V. Schurig, *Tetrahedron Lett.* **1991**, *32*, 4687–4690.
[25] X. T. Chen, Y. L. Luo, Q. B. Zhu, Z. Wang, *Chin. Chem. Lett.* **1992**, *3*, 971–973.
[26] K. J. Henry, B. Fraser-Reid, *J. Org. Chem.* **1994**, *59*, 5128–5129.
[27] N. Kanoh, J. Ishihara, A. Murai, *Synlett* **1995**, 895–897.
[28] H. Watanabe, T. Watanabe, K. Mori, *Tetrahedron* **1996**, *52*, 13939–13950.
[29] H. Watanabe, T. Watanabe, K. Mori, T. Kitihara, *Tetrahedron Lett.* **1997**, *38*, 4429–4432.
[30] H. Schlesiger, E. Winterfeldt, *Chirality* **1997**, *9*, 454–458.
[31] N. Kanoh, J. Ishihara, A. Murai, *Synlett* **1997**, 737–739.
[32] D. Haag, X. T. Chen, B. Fraser-Reid, *Chem. Commun.* **1998**, 2577–2578.
[33] a) J. Ishihara, T. Fukuzaki, A. Murai, *Tetrahedron Lett.* **1999**, *40*, 1907–1910; b) J. Ishihara, Y. Yamamoto, N. Kanoh, A. Murai, *Tetrahedron Lett.* **1999**, *40*, 4387–4390.
[34] D. Pflieger, B. Muckensturm, P. C. Robert, M. T. Simonis, J. C. Kienlen, *Tetrahedron Lett.* **1987**, *28*, 1519–1522
[35] B. Fraser-Reid, X. T. Chen, D. Haag, K. J. Henry, A. T. McPhail, *Chirality* **2000**, *12*, 488–495.
[36] Y. Yamamoto, J. Ishihara, N. Kanoh, A. Murai, *Synthesis* **2000**, 1894–1966.
[37] K. C. Nicolaou, M. Follmann, A. J. Roecker, K. W. Hunt, *Angew. Chem.* **2002**, *114*, 2207–2210; *Angew. Chem. Int. Ed.* **2002**, *41*, 2103–2106.
[38] K. C. Nicolaou, A. J. Roecker, M. Follmann, R. Baati, *Angew. Chem.* **2002**, *114*, 2211–2214; *Angew. Chem. Int. Ed.* **2002**, *41*, 2107–2110.
[39] T. Fukuzaki, T. Kobayashi, T. Hibi, Y. Ikuma, J. Ishihara, N. Kanoh, A. Murai, *Org. Lett.* **2002**, *4*, 2877–2880.
[40] K. C. Nicolaou, A. J. Roecker, H. Monenschein, P. Guntupalli, M. Follmann, *Angew. Chem.* **2003**, *115*, 3765–3770; *Angew. Chem. Int. Ed.* **2003**, *42*, 3637–3642.
[41] J. Ishihara, Y. Ikuma, S. Hatakeyama, T. Suzuki, A. Murai, *Tetrahedron* **2003**, *59*, 10287–10294.
[42] A. Murai, *J. Toxicol. Toxin Rev.* **2003**, *22*, 617–632.
[43] S. Raina, B. A. Bhanu Prasad, V. K. Singh, *Arkivoc* **2003**, 16–24.
[44] K. C. Nicolaou, P. K. Sasmal, A. J. Roecker, X. W. Sun, S. Mandal, A. Converso, *Angew. Chem.* **2005**, *117*, 3509–3513; *Angew. Chem. Int. Ed.* **2005**, *44*, 3443–3447.
[45] K. C. Nicolaou, P. K. Sasmal, T. V. Kostis, A. Converso, E. Loizidou, F. Kaiser, A. J. Roecker, C. C. Dellios, X. W. Sun, G. Petrovic, *Angew. Chem.* **2005**, *117*, 3513–3518; *Angew. Chem. Int. Ed.* **2005**, *44*, 3447–3452.
[46] H. Watanabe, N. Mori, D. Itoh, T. Kitahara, K. Mori, *Angew. Chem.* **2007**, *119*, 1534–1538; *Angew. Chem. Int. Ed.* **2007**, *46*, 1512–1516.
[47] S. V. Ley, J. C. Anderson, W. M. Blaney, E. D. Morgan, R. N. Sheppard, M. S. J. Simmonds, A. M. Z. Slawin, S. C. Smith, D. J. Williams, A. Wood, *Tetrahedron* **1991**, *47*, 9231–9246.
[48] S. V. Ley, J. C. Anderson, W. M. Blaney, P. S. Jones, Z. Lidert, E. D. Morgan, N. G. Robinson, D. Santafianos, M. S. J. Simmonds, P. L. Toogood, *Tetrahedron* **1989**, *45*, 5175–5192.
[49] H. C. Kolb, S. V. Ley, *Tetrahedron Lett.* **1991**, *32*, 6187–6190.
[50] H. C. Kolb, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735–2762.
[51] W.-J. Koot, S. V. Ley, *Tetrahedron* **1995**, *51*, 2077–2090.
[52] H. C. Brown, *J. Am. Chem. Soc.* **1966**, *88*, 1447–1452.
[53] S. V. Ley, P. J. Lovell, A. M. Z. Slawin, S. C. Smith, D. J. Williams, A. Wood, *Tetrahedron* **1993**, *49*, 1675–1700.
[54] S. V. Ley, *Pure Appl. Chem.* **1994**, *66*, 2099–2102.
[55] J. C. Anderson, S. V. Ley, D. Santafianos, R. N. Sheppard, *Tetrahedron* **1991**, *47*, 6813–6850.
[56] P. J. Lovell, PhD Thesis, University of London (UK), **1992**.
[57] H. Lovell, PhD Thesis, University of Cambridge (UK), **1994**.
[58] R. Bänteli, PostDoctoral Research Report, University of Cambridge (UK), **1994**.
[59] C. E. Gutteridge, PhD Thesis, University of Cambridge (UK), **1996**.
[60] For a review see: G. E. Veitch, A. Boyer, S. V. Ley, *Angew. Chem.* **2008**, *120*, 9542–9570; *Angew. Chem. Int. Ed.* **2008**, *47*, 9402–9429.
[61] J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[62] Decalin **21** was prepared from **16** under standard conditions (TESOTf, iPr$_2$NEt): for full details see Supporting Information.
[63] S. V. Ley, C. E. Gutteridge, A. R. Pape, C. D. Spilling, C. Zumbrunn, *Synlett* **1999**, 1295–1297.
[64] A. Q. Somers, PhD Thesis, University of Cambridge (UK), **2001**.
[65] M. Hiersemann, U. Nubbemeyer, *The Claisen Rearrangement*, Wiley-VCH, Weinheim, **2007**.
[66] Although our previous work depicted the triethylsilylether at the C1 position in compound **36** (see reference [67]), further NMR studies indicated that this assignment was incorrect. It is now clear that the silyl protecting group is attached to the C3 hydroxyl group.
[67] T. Durand-Reville, L. B. Gobbi, B. L. Gray, S. V. Ley, J. S. Scott, *Org. Lett.* **2002**, *4*, 3847–3850.
[68] S. V. Ley, *Pure Appl. Chem.* **2005**, *77*, 1115–1130.
[69] M. H. Clausen, M. R. Jorgensen, J. Thorsen, R. Madsen, *J. Chem. Soc. Perkin Trans. 1* **2001**, 543–551.
[70] S. David, S. Hanessian, *Tetrahedron* **1985**, *41*, 643–663.
[71] E. Cleator, C. F. McCusker, F. Stelzer, S. V. Ley, *Tetrahedron Lett.* **2004**, *45*, 3077–3080.
[72] B. Fraser-Reid, U. E. Udodong, Z. Wu, H. Ottosson, J. R. Merritt, S. M. Rao, C. Roberts, R. Madsen, *Synlett* **1992**, 927–942.
[73] L. C. Swallen, C. E. Boord, *J. Am. Chem. Soc.* **1930**, *52*, 651–660.
[74] C. G. Schmitt, C. E. Boord, *J. Am. Chem. Soc.* **1931**, *53*, 2427–2428.
[75] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[76] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1581.
[77] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564; b) G. J. Roth, B. Liepold, S. G. Müller, H. J. Bestmann, *Synlett* **1996**, 521–522.
[78] A. N. Rai, A. Basu, *Tetrahedron Lett.* **2003**, *44*, 2267–2269.

[79] G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7773–7776; *Angew. Chem. Int. Ed.* **2007**, *46*, 7629–7632.
[80] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979.
[81] A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[82] P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, N. Thompson, *Synthesis* **1987**, 1015–1017.
[83] G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, C. Ayats, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7777–7779; *Angew. Chem. Int. Ed.* **2007**, *46*, 7633–7635.
[84] M. Ball, S. P. Andrews, F. Wierschem, E. Cleator, M. Smith, S. V. Ley, *Org. Lett.* **2007**, *9*, 663–666.
[85] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
[86] A. A. Denholm, L. Jennens, S. V. Ley, A. Wood, *Tetrahedron* **1995**, *51*, 6591–6604.
[87] G. E. Veitch, A. Pinto, A. Boyer, E. Beckmann, J. C. Anderson, S. V. Ley, *Org. Lett.* **2008**, *10*, 569–572.

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