Pergamon

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Tetrahedron 59 (2003) 6833–6849

TETRAHEDRON

A fully stereocontrolled total synthesis of (+)-leucascandrolide A

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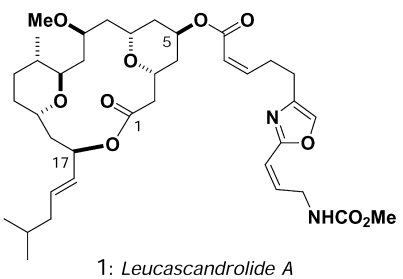
Received 28 April 2003; revised 16 May 2003; accepted 16 May 2003

Abstract—A highly stereocontrolled total synthesis of leucascandrolide A, a cytotoxic 18-membered macrolide from the calcareous sponge *Leucascandra caveolata*, starts out with a Jacobsen asymmetric hetero Diels–Alder reaction to configure the 2,6-*cis*-tetrahydropyran ring. All the remaining oxygenated stereocentres are introduced with high selectivity by relying on substrate-based control. An efficient endgame depends on two Mitsunobu reactions, the first to close the macrolactone with inversion at C17 and the second to attach the oxazole-containing side chain at C5, followed by Lindlar hydrogenation of the two alkynes to provide (+)-leucascandrolide A.

1. Introduction

Marine organisms produce a fascinating range of structurally diverse secondary metabolites, which often possess significant biological activities and have great potential as molecular probes for investigating biochemical pathways.[1] Marine-derived macrolides have attracted prominent attention in this regard.[2] Leucascandrolide A (**1**, Fig. 1) was isolated in 1996 from the New Caledonian calcareous sponge *Leucascandra caveolata* by Pietra and co-workers.[3] This highly oxygenated 18-membered macrolide has eight stereogenic centres and three alkenes, and also features two trisubstituted tetrahydropyran rings, one of these having an unusual oxazole-containing side chain axially appended at C5. At the time, this represented a breakthrough in the search for molecular diversity from the biodiversity of calcareous sponges, which have been much less investigated by marine natural products chemists than other sponge genera. While the true biosynthetic origin of this architecturally unique polyketide is unknown, it has been proposed that leucascandrolide A and its co-metabolite leucascandrolide B are products of opportunistic microbial colonization of the sponge, as a further collection of *L. caveolata* by the Pietra group did not yield any traces of either compound.[4]



1: *Leucascandrolide A*

Figure 1. Structure of leucascandrolide A.

In preliminary biological studies, leucascandrolide A exhibited potent cytotoxic activity in vitro against KB oral epidermoid carcinoma and P388 leukemia cell lines (IC_{50}=0.05 and 0.25 μg/mL, respectively), as well as significant inhibition of the pathogenic fungus *Candida albicans*.[3] Additionally, following hydrolysis of the C5 ester linkage, biological testing of the 18-membered macrocyclic core and the separated side chain demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity, while the oxazole-containing unsaturated side chain appears to be responsible for the antifungal activity.

As a consequence of the natural supply of leucascandrolide A (**1**) being extremely limited, if not entirely exhausted due to the failure to reisolate it, a flexible and efficient synthesis is essential for further biological studies, while also opening access to de novo analogues. Due to its challenging and unusual polyketide structure and interesting biological profile, leucascandrolide A has attracted considerable synthetic attention from several groups,[5–8] with the first total synthesis reported by Leighton and co-workers.[6a] Recently, we disclosed our successful route to (+)-leucascandrolide A,[5] and we now report full details of the evolution of our initial formal synthesis and the steps leading to the completion of a total synthesis by the preparation and attachment of the oxazole-containing side chain.

Keywords: macrolides; hetero Diels–Alder reaction; aldol reaction; Mitsunobu reaction; cytotoxic; antifungal.
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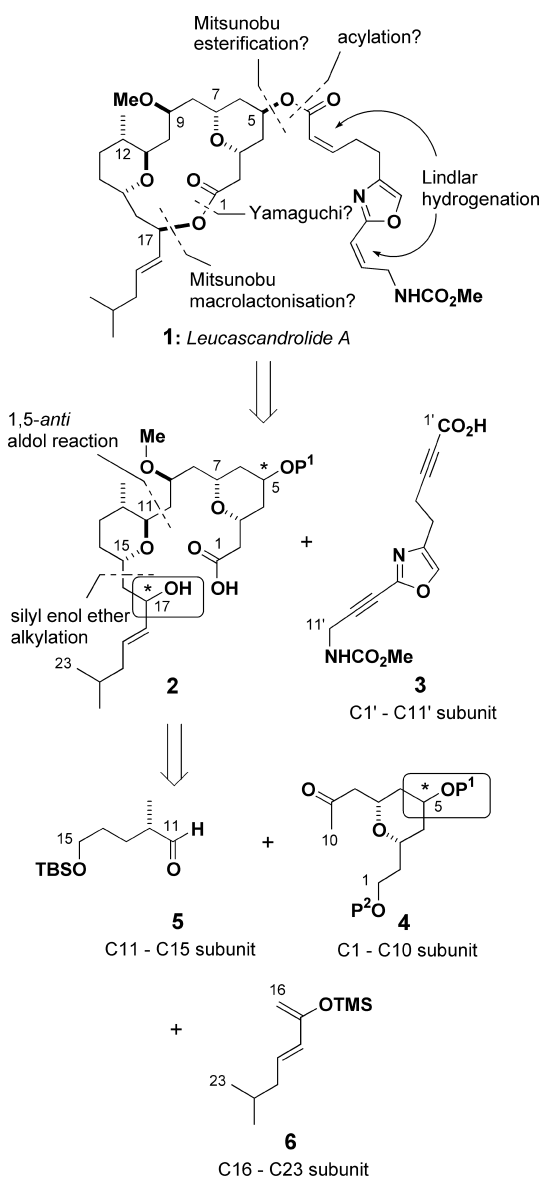
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00814-7

2. Retrosynthetic analysis and general synthetic strategy

As outlined in Scheme 1, two late-stage esterification steps were envisaged as part of an appropriate endgame to access leucascandrolide A (**1**). The first would involve the macrolactonisation of *seco*-acid **2**, while the second would be employed to append the unsaturated side chain using the oxazole containing acid **3**, which contains two alkyne groups. In the final step, a double Lindlar hydrogenation was anticipated to reduce these alkynes to install the two (*Z*)-configured alkenes stereospecifically to provide **1** directly. In order to have the option of performing a conventional acylation or a Mitsunobu-type inversion protocol, we planned to control the C5 and C17 stereocentres in either sense by appropriate ketone reductions. Importantly, we envisaged that the configuration of these two hydroxyl-bearing stereocentres could be inverted as required, providing considerable flexibility in the synthetic route. By exploiting the 1,3-dioxygenation pattern, arising from a characteristic polyketide biosynthetic pathway, we planned to introduce the oxygenated stereocentres at C9, C11 and C15 using suitable substrate-controlled reactions. Recognising the 1,5-*anti* relationship between the C7 and C11 stereocentres, the *seco*-acid **2** (with either (*R*)- or (*S*)-configuration at C5 and C17) should be accessible by a strategic aldol coupling step performed between the methyl ketone **4** (with either (*R*)- or (*S*)-configuration at C5) and aldehyde **5**, as a suitable C11–C15 subunit, using methodology developed in our laboratory.[9,10] Furthermore, the newly created C11 stereocentre could, in turn, direct an anomeric alkylation with silyl enol ether **6**, as a suitable C16–C23 subunit, thus configuring the C15 centre in **2** and installing C17 initially as a ketone. However, two additional considerations were identifying a reliable method for the asymmetric synthesis of the 2,6-*cis*-tetrahydropyran with introduction of the C3 and C7 stereocentres, as required for the generalised C1–C10 subunit **4**, and a workable route to preparing the proposed oxazole-containing C1′–C11′ subunit **3**. As indicated in the following account, this general plan, with the selection of suitable protecting groups, served us well and provided sufficient flexibility in defining the optimum ordering of the steps.



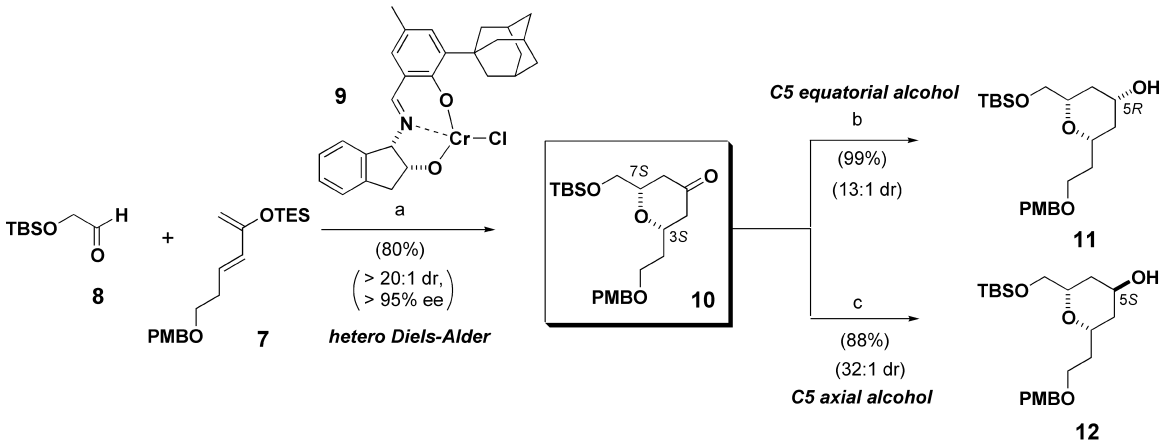
Scheme 1. Retrosynthetic analysis for leucascandrolide A leading to key building blocks.

3. Results and discussion

In initiating our synthetic efforts, we turned to exploring the use of the recently reported Jacobsen hetero Diels–Alder reaction[11] for constructing the right-hand tetrahydropyran ring of leucascandrolide A, simultaneously configuring the C3 and C7 stereocentres (Scheme 2). For access to the proposed C1–C10 subunit **4**, this involved starting out from the readily available 2-silyloxydiene **7** (obtained by silyl enol ether formation from the corresponding enone[12]) and aldehyde **8**. Thus, treatment of a neat mixture of diene **7** and aldehyde **8** with the chiral tridentate chromium-(III) catalyst **9** (10 mol%, 4 Å molecular sieves) for 20 h afforded, after mild acidic work-up to hydrolyse the initially formed [4+2]-cycloadduct, the required 2,6-*cis*-tetrahydropyran **10** in 80% yield. After optimisation, this hetero Diels–Alder reaction[13] proved reasonably scaleable and proceeded with (>20:1 dr and, importantly, delivered the desired (3*S*,7*S*)-configuration with (>95% ee (as determined by later Mosher ester analysis).

Although we assumed the C5 configuration could be inverted if required at the macrocycle stage, to cover every eventuality both alcohols **11** and **12** were prepared. To this end, reduction of ketone **10** with $NaBH_4$ in MeOH afforded the C5-equatorial alcohol **11** (99%, 13:1 dr), while treatment of **10** with L-Selectride® in THF provided the axial epimer **12** with high selectivity (88%, 32:1 dr).

The C5-equatorial isomer **11** was initially selected to progress through the synthesis in order to evaluate the later chemistry. As shown in Scheme 3, the alcohol **11** was first converted into its TIPS derivative and the TBS ether was cleaved selectively under acidic methanolysis conditions to afford alcohol **13**. In order to homologate the C7 substituent on the tetrahydropyran ring, alcohol **13** was activated as its triflate derivative (Tf_2O, pyr, CH_2Cl_2) which enabled clean nucleophilic displacement with lithium



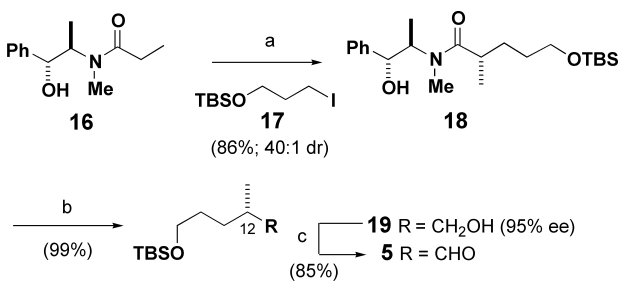
Scheme 2. (a) 4 Å molecular sieves, 20°C, 20 h; acidified $CHCl_3$, 20°C, 4 h; (b) $NaBH_4$, MeOH, 0°C, 1 h; (c) L-Selectride®, THF, −100°C, 1.5 h.

trimethylsilylacetylide, in the presence of HMPA, followed by basic methanolysis to provided the alkyne **14** (81%).[14] Finally, mercury-(II) mediated hydration of the terminal alkyne generated the methyl ketone **15**, which was essentially enantiopure. Notably, this efficient reaction sequence was performed to produce multigram quantities of the C1–C10 subunit **15**.

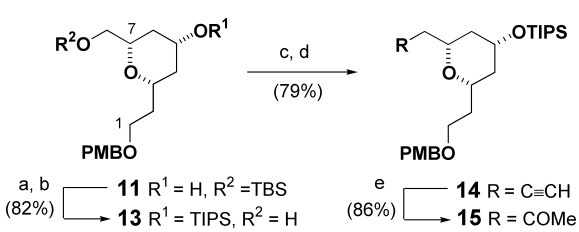
Preparation of the C11–C15 aldehyde **5** commenced from the Myers chiral amide **16** and the iodide **17**, where the C12 stereocentre was installed by a diastereoselective enolate alkylation.[15] Thus, enolisation of **16** with LDA in THF, in the presence of LiCl, and addition of **17** afforded the amide **18** cleanly (86%, ≥40:1 dr). Next, the chiral auxiliary was reductively cleaved using lithium amidoborane to provide the alcohol **19** in 99% yield and ≥95% ee (Mosher ester analysis). This was oxidised with Dess–Martin periodinane to the required aldehyde **5** (85%) and used directly in the next step (Scheme 4).

We now turned to forming the C10–C11 bond with concomitant generation of the C11 stereocentre under the directing influence of the remote C7 oxygenated centre (Scheme 5). This pivotal 1,5-*anti* aldol bond construction between the β-oxygenated ketone **15** and the (*S*)-configured aldehyde **5** proceeded smoothly using the kinetically generated boron enolate under our reported conditions.[9a,16] Thus, treatment of methyl ketone **15** with *c*-Hex_2BCl, in the presence of Et_3N in Et_2O, resulted in regiocontrolled formation of the less substituted dicyclohexylboron enolate **20**, which on reaction with aldehyde **5** provided the desired aldol adduct **21** in 99% yield and 17:1 dr. Notably, analogous reactions with achiral aldehydes gave comparable levels of 1,5-stereoinduction from the enolate component **20**, indicating that the chiral aldehyde **5** was not contributing any significant 1,2-stereoinduction in setting up the C11 centre in this complex aldol coupling. Moreover, this result is fully consistent with our earlier studies[9] and related work from the Evans group.[10]

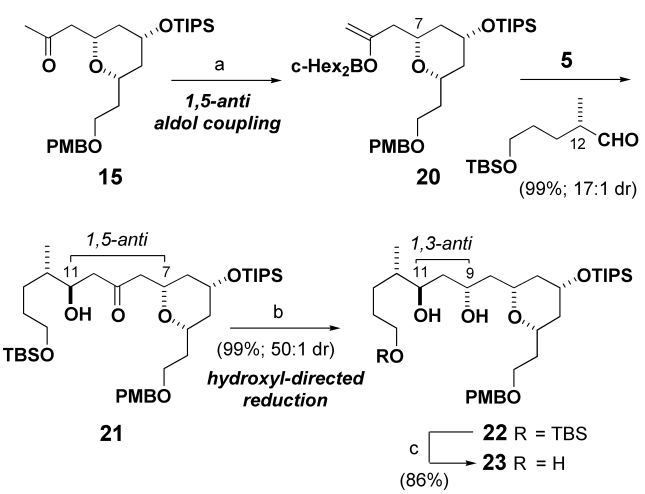
Next, the newly introduced C11 stereocentre was used to control the introduction of the neighbouring C9 centre by employing $Me_4NBH(OAc)_3$ to conduct a hydroxyl-directed, 1,3-*anti* reduction of the ketone.[17] This afforded diol **22** cleanly (99%, ≥50:1 dr) which, following cleavage of the



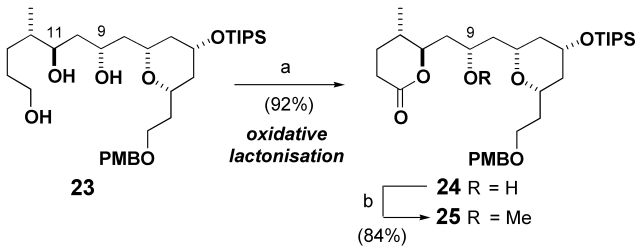
Scheme 4. (a) LDA, LiCl, THF, 0°C; (b) LDA, BH_3NH_3, THF, 0°C; (c) Dess–Martin periodinane, CH_2Cl_2, 20°C.



Scheme 3. (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 2 h; (b) CSA, 2:1 MeOH/CH_2Cl_2, 20°C, 1 h; (c) Tf_2O, pyr, CH_2Cl_2, −10°C, 1 h; (d) LDA, TMSC≡CH, THF, HMPA, −78 to 20°C, 1 h; K_2CO_3, MeOH, 20°C, 12 h; (e) cat. $Hg(OAc)_2$, PPTS, wet THF, 40°C, 1 h.



Scheme 5. (a) *c*-Hex_2BCl, NEt_3, Et_2O, 0°C; **5**, −78 to −30°C; (b) $Me_4NBH(OAc)_3$, 3:1 MeCN/AcOH, −40 to −20°C; (c) CSA, 2:1 MeOH/CH_2Cl_2, 20°C.



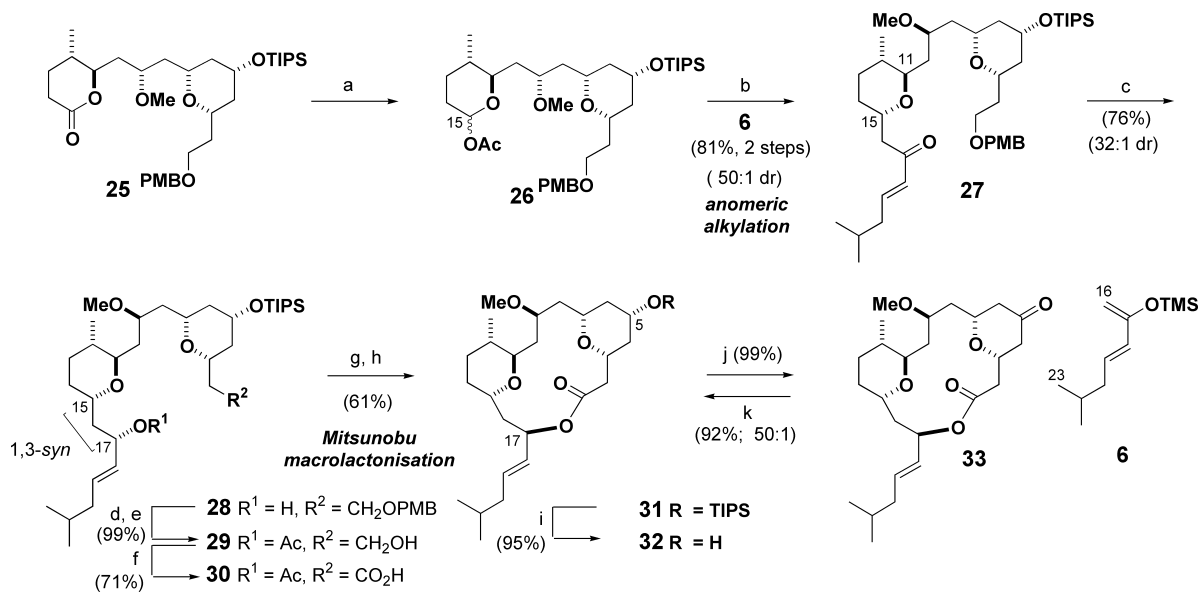
Scheme 6. (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20°C; (b) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 to 20°C.

TBS ether (CSA, MeOH), provided the 1,5,7-triol **23**. A chemoselective δ-lactonisation was now required to introduce the second tetrahydropyran ring of leucascandrolide A. Gratifyingly, this was conveniently achieved using a novel oxidative cyclisation (Scheme 6), where selective oxidation of the primary alcohol led to lactol formation and further oxidation generated the δ-lactone **24**.[5,18] Thus, prolonged treatment of triol **23** with TEMPO, in the presence of iodobenzene diacetate as re-oxidant,[19] provided lactone **24** in 92% yield. This constitutes one of the first examples of this TEMPO-mediated procedure being used for the differentiation of elaborate open-chain polyols. The remaining C9 hydroxyl group was then transformed into its methyl ether (Me_3OBF_4, Proton sponge®) to give **25** (84%).

With advanced intermediate **25** in hand, all that remained to complete the 18-membered macrolide core of leucascandrolide A was installation of the C15 side chain and macrocyclisation, where a final inversion of the C5 hydroxyl-bearing stereocentre would constitute a formal synthesis. An effective anomeric allylation approach had been utilised by Leighton and co-workers[6a] to configure the C15 stereocentre, however, following ozonolysis to give the aldehyde and an alkenyl organozinc addition, only moderate levels of control were exerted over the C17 stereocentre. As shown in Scheme 7, we opted to install the full C15 side chain via an anomeric alkylation using the silyl enol ether **6**, representing a complete C16–C23 subunit, then subsequently configure the C17 stereocentre by a suitable ketone reduction.

Lactone **25** was first reduced to the lactol with DIBAL, then acetylated in situ[20] (Ac_2O, pyr, DMAP) to provide the anomeric acetate **26** which was then treated with the silyl enol ether **6**,[21] in the presence of the mild Lewis acid $ZnBr_2$,[22] to afford enone **27** cleanly (81%, ≥50:1 dr), by presumed axial attack on the intermediate oxocarbenium ion, leading to the desired 2,6-*trans* substitution of the tetrahydropyran ring. Since the configuration of the C17 hydroxyl stereocentre could either be inverted by a Mitsunobu-type macrocyclisation, or retained by using a more conventional Yamaguchi-type macrolactonisation, effort was focused on developing a highly selective reduction in either stereochemical sense. After screening a range of reagents and conditions, we found that reduction by $LiAlH(Ot\text{-}Bu)_3$ in CH_2Cl_2 afforded the 1,3-*syn* allylic alcohol **28** in 76% yield with a diastereomeric ratio of ≥32:1. This high level of 1,3-stereoinduction may be a simple consequence of lithium chelation with the C15 ether oxygen or operation of the Evans polar model.[23]

Next, the resulting C17 hydroxyl in **28** was temporarily converted into its acetate derivative (Ac_2O, pyr, DMAP) and the PMB ether oxidatively cleaved (DDQ) to afford alcohol **29** (99%). Subsequent oxidation of alcohol **29** to the corresponding acid **30** (TEMPO/$PhI(OAc)_2$ then $NaClO_2$),[19] followed by hydrolysis of the acetate (K_2CO_3, MeOH), provided the corresponding *seco*-acid, in readiness for the challenging Mitsunobu macrocyclisation to invert the C17 centre. Gratifyingly, by using Mitsunobu macrolactonisation conditions, as developed in the context of our earlier total synthesis of laulimalide,[24,25] the *seco*-acid was treated with DEAD in benzene, in the presence of excess PPh_3, to afford the 18-membered macrolide **31** in 61% yield.



Scheme 7. (a) DIBAL, CH_2Cl_2; Ac_2O, pyr. DMAP, −78 to −20°C; (b) $ZnBr_2$, CH_2Cl_2, 0°C; (c) $LiAlH(Ot\text{-}Bu)_3$, CH_2Cl_2, −78 to −10°C; (d) Ac_2O, Pyr, DMAP, CH_2Cl_2, 0 to 20°C; (e) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20°C; (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20°C; $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*-BuOH, 0 to 20°C; (g) K_2CO_3, MeOH, 20°C; (h) DEAD, PPh_3, PhH, 20°C; (i) HF.Pyr, THF, 0 to 20°C; (j) Dess–Martin periodinane, pyr, CH_2Cl_2, 20°C.

Extensive NMR analysis revealed that this cyclisation proceeded with clean inversion and without any competing allylic rearrangement. Finally, the TIPS ether was cleaved using HF·pyr in THF to provide the C5-equatorial macrolide **32** (95%).

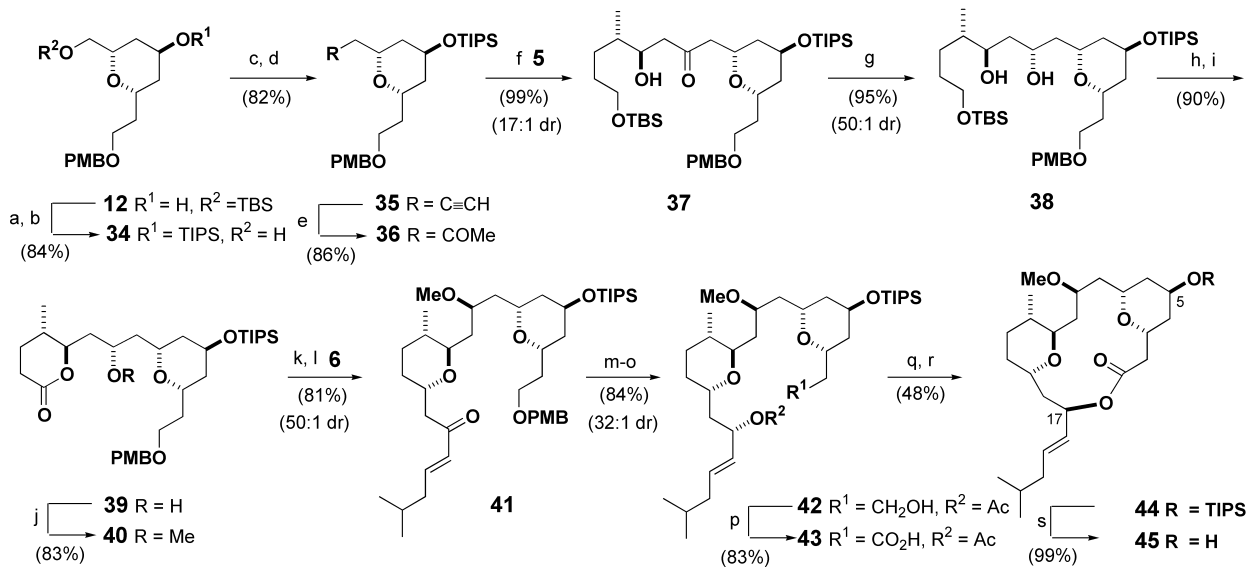
At this point, studies into the preparation of the C1′–C11′ oxazole side chain **3**, as required for a projected Mitsunobu-type acylation at C5, were still in their infancy. As a consequence of this, efforts were initially focused on inverting the C5 configuration by oxidation and subsequent reduction by equatorial hydride attack, thus securing a formal synthesis. Whilst Dess–Martin oxidation of alcohol **32** proceeded smoothly to afford ketone **33**, subsequent reduction with L-Selectride® surprisingly afforded only the returned C5-equatorial macrocycle **32**. Presumably, the unexpected preference for apparent axial attack on the pyranone ring by a sterically encumbered reducing agent, such as L-Selectride®, arises here from the macrocyclic conformational bias of **33**.[26]

With this last frustrating result and our stocks of advanced intermediates in the C5-equatorial series now substantially depleted, we decided to go back and access the required C5-*epi* macrolide core from the already prepared C5-axial tetrahydropyran **12** (Scheme 2). As summarised in Scheme 8, by using the optimised route developed in the C5-equatorial series, **12** was first transformed into alcohol **34** (93%). Next, **34** was activated as its triflate derivative, displaced with lithium trimethylsilylacetylide, and subjected to basic methanolysis to provide alkyne **35**. Subsequent hydrative oxymercuration then generated the desired C1–C10 ketone **36** in 63% yield over 3 steps.

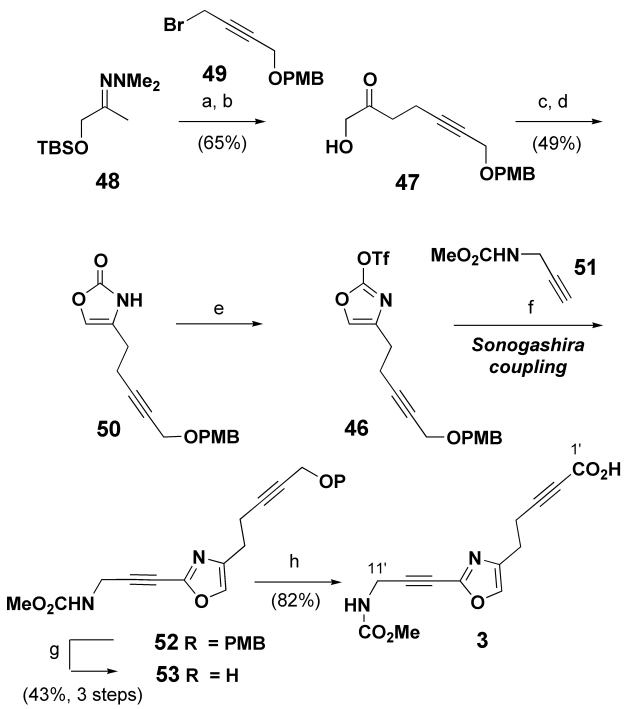
As in the C5-equatorial series, the ketone **36** was coupled with aldehyde **5** using our boron-mediated 1,5-*anti* aldol methodology. Again, enolisation of ketone **36** (*c*-Hex_2BCl, Et_3N, Et_2O) followed by addition of aldehyde **5** provided aldol adduct **37** smoothly (99%, 17:1 dr). Next, an Evans–Saksena reduction[17] provided alcohol **38** (95%, ≥50:1 dr), which following acidic cleavage of the TBS ether (HCl, MeOH, 94%), was subjected to the TEMPO-mediated oxidative cyclisation protocol to afford δ-lactone **39** (90%). Finally, *O*-methylation (Me_3OBF_4, Proton-Sponge®) gave key intermediate **40** in 83% yield.

To complete the synthesis of the C5-axial macrolide all that now remained was the installation of the appropriate C15 side chain followed by macrocyclisation. By relying on the previously developed chemistry, lactone **40** was reduced to the corresponding lactol, acetylated in situ and subjected to our anomeric alkylation conditions with silyl enol ether **6** to afford enone **41** (81%, ≥50:1 dr). Subsequent 1,3-*syn* reduction ($LiAlH(Ot\text{-}Bu)_3$, ≥32:1 dr) was followed by *O*-acetylation (Ac_2O, pyr, DMAP) and oxidative removal (DDQ) of the PMB group to provide alcohol **42** (84%). Next, alcohol **42** was oxidised to the corresponding acid **43** and the C15 acetate hydrolysed to reveal the *seco*-acid. Treatment of this *seco*-acid under our optimised Mitsunobu conditions (DEAD, PPh_3, degassed PhH) afforded macrolide **44** in 48% yield. Finally, the TIPS ether was cleaved (TBAF, THF) to provide the C5-axial alcohol **45** in 99% yield. At this point, our spectroscopic data for **45** matched with that reported by the groups of Pietra[3] and Leighton[6a] for the macrocyclic core, indicating that we had now achieved a formal synthesis of (+)-leucascandrolide A.

With the two macrolides **32** and **45** in hand, attention was now focused on the preparation of the oxazole-containing side chain **3** in order to explore the viability of our planned endgame (cf. Scheme 2) to deliver leucascandrolide A. As shown in Scheme 9, key to the preparation of side chain **3** was a Sonogashira coupling step,[27] where the required oxazole triflate **46** was derived from ketone **47**, the



Scheme 8. (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78°C; (b) CSA, 2:1 MeOH/CH_2Cl_2, 20°C; (c) Tf_2O, pyr, CH_2Cl_2, −10°C; (d) LDA, TMSC≡CH, THF, HMPA, −78 to 20°C; K_2CO_3, MeOH, 20°C; (e) cat. $Hg(OAc)_2$, PPTS, wet THF, 40°C; (f) *c*-Hex_2BCl, NEt_3, Et_2O, 0°C; **5**, −78 to −30°C; (g) $Me_4NBH(OAc)_3$, 3:1 MeCN/AcOH, −40 to −20°C; (h) HCl, MeOH/CH_2Cl_2, 25°C; (i) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20°C; (j) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 to 20°C; (k) DIBAL, CH_2Cl_2; Ac_2O, pyr. DMAP, −78 to −20°C; (l) $ZnBr_2$, CH_2Cl_2, 0°C; (m) $LiAlH(Ot\text{-}Bu)_3$, CH_2Cl_2, −78 to −10°C; (n) Ac_2O, Pyr, DMAP, CH_2Cl_2, 0 to 20°C; (o) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20°C; (p) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20°C; $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*-BuOH, 0 to 20°C; (q) K_2CO_3, MeOH, 20°C; (r) DEAD, PPh_3, PhH, 20°C; (s) TBAF, THF, 0°C.

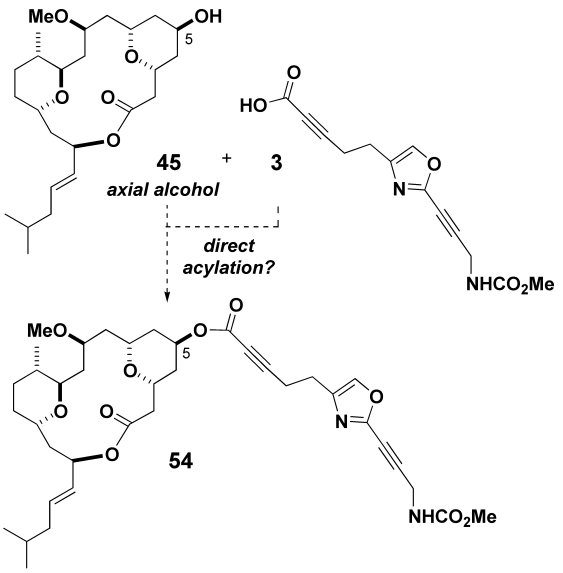


Scheme 9. (a) LDA, HMPA, THF, −78 to 20°C; (b) TBAF, THF, 20°C; (c) $Cl_3CC(O)NCO$, CH_2Cl_2, 20°C; K_2CO_3, MeOH, 20°C; (d) 4 Å molecular sieves, PhMe, 90°C; (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 to −10°C; (f) $Pd(PPh_3)_4$, **42**, 2,6-lutidine, 1,4-dioxan, 20°C; (g) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20°C; (h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20°C; $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*-BuOH, 0 to 20°C.

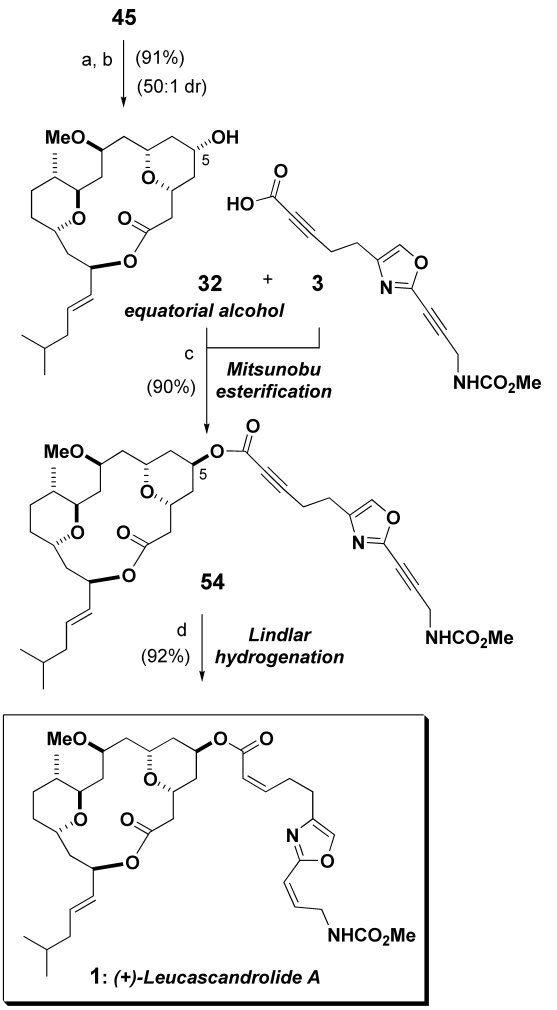
α-alkylation product of the *N*,*N*-dimethylhydrazone **48**[28] with the propargylic bromide **49**[29] (LDA, THF, HMPA) followed by TBS ether cleavage (TBAF). Treatment of the α-hydroxy ketone **47** with trichloroacetyl isocyanate, followed by basic hydrolysis and heating the resulting inseparable mixture to 90°C, in the presence of 4 Å molecular sieves, produced the required oxazolone **50** (49%). Reaction of **50** with Tf_2O in the presence of 2,6-lutidine then provided oxazole triflate **46**, which was reacted with alkyne **51**[6a] under the Sonogashira coupling conditions ($Pd(PPh_3)_4$, CuI, 2,6-lutidine, 1,4-dioxane) developed by Panek and co-workers,[30] to provide the corresponding side chain precursor **52**. Removal of the PMB group (DDQ), followed by oxidation of the resulting alcohol **53** to the carboxylic acid (TEMPO/$PhI(OAc)_2$; $NaClO_2$), then gave the required C1′–C11′ subunit **3** in 36% yield over 5 steps.

Following the successful preparation of the required C1′–C11′ subunit **3**, the most obvious way to reach (+)-leucascandrolide A appeared to be via direct acylation of the C5-axial macrolide **45**, followed by Lindlar hydrogenation of the expected ester **54** to configure the two (*Z*)-alkenes (Scheme 10). However, what at first was considered to be the simpler approach met with difficulties from the onset, presumably due to the hindered nature of the C5 axial alcohol. Under a range of acylation conditions, employing various activated acid derivatives of **3**, or the corresponding acid chloride, only recovered macrolide **45** could be obtained.

Following this disappointing outcome, our efforts turned to examining the alternative option of performing a Mitsunobu



Scheme 10. Direct acylation route.



Scheme 11. (a) Dess–Martin periodinane, pyr, CH_2Cl_2, 20°C; (b) L-Selectride®, THF, −100°C; (c) DEAD, PPh_3, 1.5:1 THF/PhMe, 0 to 20°C; b) H_2, 5% $Pd/CaCO_3$ poisoned with lead (Lindlar catalyst), quinoline, EtOAc, 20°C.

esterification between the C5-equatorial macrolide **32** and side chain **3** (Scheme 11). To increase our stocks of material in this series, the remaining C5-axial macrolide **45** could readily be converted into the C5-equatorial macrolide **32** in 91% yield by the oxidation/reduction sequence (Dess Martin periodinane; L-Selectride®) already established (cf. Scheme 4). To our delight, reaction of the side-chain acid **3** and macrocycle **32**, in the presence of excess DEAD and PPh_3, facilitated the smooth formation of coupled product **54** in 90% yield. Finally, double Lindlar hydrogenation of the two triple bonds proceeded without incident, affording (+)-leucascandrolide A; $[\alpha]_D^{20}$=+40.0 (*c*=0.29, EtOH), in 92% yield with clean installation of both (*Z*)-alkenes. The physical and spectroscopic data for this synthetic material[31] were identical in every respect to that reported by Pietra[3] and Leighton.[6a]

4. Conclusions

In summary, we have developed an efficient total synthesis of (+)-leucascandrolide A that proceeds in 23 steps and 6% overall yield from diene **7** and is characterised by essentially complete stereochemical control. Key features include a Jacobsen asymmetric hetero Diels–Alder reaction to configure the right-hand tetrahydropyran ring, the development of novel oxidative cyclisation methodology for the construction of lactone motifs, along with efficient anomeric alkylation protocols for their subsequent elaboration, as well as further illustrations of the utility of our 1,5-*anti* aldol methodology and the Mitsunobu reaction for complex polyketide synthesis. Finally, we believe that this synthetic route to (+)-leucascandrolide A could be developed to provide useful quantities of this rare marine natural product, as well as a range of structural analogues.

5. Experimental

5.1. Data for compounds

5.1.1. Diene 7. To a cold (0°C), stirred solution of (*E*)-6-(4-methoxybenzyloxy)-hex-3-en-2-one[12] (4.40 g, 18.8 mmol), in dry Et_2O (88 mL), was added triethylsilyl trifluoromethylsulfonate (5.10 mL, 22.5 mmol) followed by Et_3N (3.40 mL, 24.4 mmol). After stirring for 1.5 h, the reaction mixture was filtered through a plug of dry alumina (eluting with Et_2O) and the filtrate concentrated in vacuo to give diene **7** (6.18 g, 95%), which was used without further purification; R_f 0.75 (20% EtOAc/40–60 petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.87 (2H, d, *J*=8.6 Hz), 6.04 (1H, dt, *J*=15.3, 6.4 Hz), 5.94 (1H, br d, *J*=15.3 Hz), 4.45 (2H, s), 4.26 (1H, br s), 4.20 (1H, br s), 3.80 (3H, s), 3.51 (2H, t, *J*=6.9 Hz), 2.41 (2H, br q, *J*=6.8 Hz), 1.00 (9H, t, *J*=8.2 Hz), 0.73 (6H, t, *J*=8.2 Hz).

5.1.2. Pyranone 10. To a cold (0°C), stirred mixture of aldehyde **8** (656 μL, 3.44 mmol), tridentate chromium catalyst **9** (50 mg, 0.10 mmol), as prepared by the method of Jacobsen from (1*S*,2*R*)-*cis*-1-amino-2-indanol,[11] and 4 Å molecular sieves (330 mg), was added diene **7** (600 mg, 450 μL, 10.2 mmol). After warming to room temperature, the reaction mixture was stirred for 12 h, diluted with CH_2Cl_2, and filtered through a plug of $MgSO_4$. The organic filtrate was concentrated in vacuo, dissolved in acidified chloroform† (10 mmol) and stirred for 4 h. The reaction mixture was then treated with Et_3N (139 μL, 1.00 mmol) and concentrated in vacuo. Flash chromatography (20% Et_2O/40–60 petroleum ether) afforded the pyranone **10**‡ as a light yellow oil (562 mg, 80%); R_f=0.45 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−16.4 (*c*. 2.5, $CHCl_3$); ν_{max}, cm^{-1} (film) 2942, 2910, 2856, 1720, 1610, 1245; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J*=8.5 Hz), 6.87 (2H, d, *J*=8.5 Hz), 4.43 (1H, d, *J*=11.7 Hz), 4.40 (1H, d, *J*=11.7 Hz), 3.80 (3H, s), 3.79–3.76 (1H, m), 3.73–3.69 (1H, m), 3.67–3.62 (1H, m), 3.61–3.53 (1H, m), 2.39–2.32 (3H, m), 2.24 (1H, dd, *J*=14.3, 11.7 Hz), 1.94–1.88 (1H, m), 1.84–1.77 (1H, m), 0.89 (9H, s), 0.06 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.5, 159.2, 130.4, 129.2, 113.8, 77.2, 74.1, 72.7, 65.8, 55.3, 47.8, 44.1, 36.4, 25.9, 20.6, 18.3, −5.3, −5.3; *m*/*z* (CI+) 426 ($[M+NH_4]^+$, 10%); HRMS (ES+) Found 426.2666, $[C_{22}H_{40}NO_5Si]^+$ requires 426.2676.

5.1.3. Alcohol 11. To a stirred solution of pyranone **10** (4.50 g, 11.0 mmol), in MeOH (90 mL), at room temperature, was added sodium borohydride (540 mg, 14.2 mmol). After stirring for 1 h, the reaction mixture was decanted into sat. aqueous NH_4Cl (100 mL), brine (100 mL) and Et_2O (100 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Preliminary flash chromatography (20% Et_2O/30–40 petroleum ether) afforded alcohol **11** (4.50 g, 99%; 13:1 dr). Further flash chromatography (10% Et_2O/30–40 petroleum ether) afforded pure equatorial alcohol **11** (4.18 g, 93%) as a colourless oil; R_f=0.36 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−21.0 (*c*. 1.3, $CHCl_3$); ν_{max}, cm^{-1} (film) 3412, 2932, 2845, 1605, 1245; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.4 Hz), 6.87 (2H, d, *J*=8.4 Hz), 4.45 (2H, br s), 3.84–3.82 (4H, m), 3.68 (1H, dd, *J*=10.3, 5.4 Hz), 3.61–3.50 (4H, m), 3.40–3.36 (1H, m), 2.04–2.01 (1H, m), 1.94–1.91 (1H, m), 1.85–1.80 (1H, m), 1.77–1.72 (1H, m), 1.45 (1H, d, *J*=4.4 Hz), 1.19–1.09 (2H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.2, 130.7, 129.2, 113.8, 76.2, 72.7, 72.6, 68.2, 66.4, 66.3, 55.3, 41.4, 37.8, 36.2, 25.9, 18.3, −5.2, −5.3; *m*/*z* (CI+) 411 ($[M+H]^+$, 20%), 428 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 428.2829, $[C_{22}H_{42}NO_5Si]^+$ requires 428.2832.

5.1.4. Alcohol 12. To a cold (−100°C), stirred solution of pyranone **10** (4.0 g, 9.8 mmol), in THF (100 mL), was added L-Selectride® (14.7 mL, 14.7 mmol, 1 M in THF). After 2 h, the reaction mixture was treated with sat. aqueous NH_4Cl (100 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in

† Chloroform (300 mL) and conc. HCl (300 mL) were stirred vigorously for 1 h after which the phases were separated to give the acidified chloroform layer.

‡ There was no detectable *trans*-isomer from analysis of the crude reaction product. The enantiomeric purity of **10** was determined as (95% ee by Mosher ester analysis of the derived equatorial alcohol **11**.

vacuo. Flash chromatography (15% Et_2O/30–40 petroleum ether) afforded axial alcohol **12** (3.5 g, 88%) as a colourless oil; R_f=0.36 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−19.1 (*c*. 6.6, $CHCl_3$); ν_{max}, cm^{-1} (film) 3433, 2943, 2856, 1612, 1246; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.6 Hz), 6.87 (2H, d, *J*=8.6 Hz), 4.42 (2H, br s), 4.27–4.25 (1H, m), 3.95–3.89 (1H, m), 3.83–3.80 (4H, m), 3.64 (1H, dd, *J*=10.5, 5.4 Hz), 3.58–3.55 (2H, m), 3.50 (1H, dd, *J*=10.5, 5.4 Hz), 1.80–1.73 (1H, m), 1.72–1.58 (3H, m), 1.50–1.42 (2H, m), 1.35 (1H, d, *J*=2.8 Hz), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.2, 129.6, 129.5, 114.1, 73.0, 72.7, 69.0, 67.1, 67.0, 64.9, 55.6, 39.2, 36.7, 35.5, 26.3, 18.8, −4.8, −4.8; *m/z* (CI+) 411 ($[M+H]^+$, 10%), 428 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 411.2567, $[C_{22}H_{39}O_5Si]^+$ requires 411.2567.

5.1.5. Alcohol 13. To a cold (−78°C), stirred solution of alcohol **11** (4.07 g, 9.92 mmol), in CH_2Cl_2 (80 mL), was added 2,6-lutidine (2.85 mL, 24.5 mmol) followed by triisopropylsilyl trifluoromethylsulfonate (4.00 mL, 14.7 mmol). After 3 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (100 mL), warmed to room temperature, and the organic phase separated. The aqueous phase was extracted with Et_2O, the combined organic extracts dried ($MgSO_4$), and the solvent removed in vacuo. Flash chromatography (10% Et_2O/30–40 petroleum ether) afforded the intermediate *bis*-silyl ether (5.16 g, 93%) as a colourless oil; R_f=0.61 (20% EtOAc/40–60 petroleum ether), which was taken on to the next step. To a stirred solution of the *bis*-silyl ether (5.1 g, 9.01 mmol) in CH_2Cl_2 (33 mL) and MeOH (66 mL) was added 10-camphorsulfonic acid (209 mg, 0.90 mmol). After 3 h, the reaction mixture was treated with Et_3N (139 μL, 1.00 mmol) and concentrated in vacuo. Flash chromatography (40% Et_2O/30–40 petroleum ether) afforded alcohol **13** (3.57 g, 88%) as a colourless oil; R_f=0.16 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−7.7 (*c*. 1.32, $CHCl_3$); ν_{max}, cm^{-1} (film) 3455, 2942, 2856, 1611, 1245; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.4 Hz), 6.87 (2H, d, *J*=8.4 Hz), 4.44 (1H, d, *J*=11.6 Hz), 4.42 (1H, d, *J*=11.6 Hz), 3.93–3.85 (1H, m), 3.80 (3H, s), 3.61–3.49 (5H, m), 3.35–3.33 (1H, m), 1.95–1.71 (5H, m), 1.31–1.20 (2H, m), 1.04 (21H, m); *m/z* (CI+) 453 ($[M+H]^+$, 30%), 470 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 453.3046, $[C_{25}H_{45}O_5Si]^+$ requires 453.3036.

5.1.6. Alcohol 34. Prepared from alcohol **12** in 93% yield via the procedure described for **13**. R_f=0.17 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−4.3 (*c*. 1.32, $CHCl_3$); ν_{max}, cm^{-1} (film) 3455, 2943, 2866, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 4.45 (1H, d, *J*=11.5 Hz), 4.40 (1H, d, *J*=11.5 Hz), 4.32–4.29 (1H, m), 4.02–4.00 (1H, m), 3.97–3.94 (1H, m), 3.80 (3H, s), 3.59–3.55 (3H, m), 3.46–3.44 (1H, m), 2.00 (1H, dd, *J*=7.9, 4.4 Hz), 1.81–1.77 (1H, m), 1.72–1.67 (2H, m), 1.51 (1H, td, *J*=13.3, 2.41 Hz), 1.47–1.37 (2H, m), 1.05 (21H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 159.1, 130.7, 129.1, 113.7, 72.6, 72.1, 69.1, 66.7, 66.3, 64.9, 55.2, 39.7, 36.3, 35.2, 18.1, 12.2; *m/z* (*EI*+) 452 ($[M]^+$, 100%), (CI+) 453 ($[M+H]^+$, 100%), 470 ($[M+NH_4]^+$, 60%); HRMS (ES+) Found 453.3032, $[C_{25}H_{45}O_5Si]^+$ requires 453.3036.

5.1.7. Alkyne 14. To a cold (−10°C), stirred solution of alcohol **13** (100 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added pyridine (30 μL, 0.33 mmol) followed by trifluoromethanesulfonic anhydride (52 μL, 0.31 mmol). After 1 h, the reaction mixture was filtered through a plug of silica gel (eluting with 50% Et_2O/30–40 petroleum ether), the filtrate concentrated in vacuo and the residue azeotroped with benzene (3×2 mL) to afford the corresponding triflate which was taken on to the next step. To a cold (−78°C), stirred solution of diisopropylamine (107 μL, 0.77 mmol) in THF (3 mL) and HMPA (133 μL, 0.77 mmol) was added *n*-butyl lithium (481 μL, 0.77 mmol, 1.6 M in hexanes). The mixture was warmed to −10°C and stirred for 30 min then recooled to −78°C and treated with trimethylsilylacetylene (109 μL, 0.77 mmol). After 15 min, a solution of the prepared triflate in THF (1.5 mL) was added to the stirred mixture. After 1 h, the reaction mixture was warmed to room temperature, stirred for a further 15 min and treated with sat. aqueous NH_4Cl (3 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (4×5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give the intermediate alkyne which was taken on to the next step. To a solution of the alkyne in MeOH (5 mL) was added K_2CO_3 (41 mg, 0.30 mmol). After stirring for 12 h, the reaction mixture was treated with brine (5 mL) and Et_2O (10 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% Et_2O/30–40 petroleum ether) afforded alkyne **14** (85 mg, 84%) as a colourless oil; R_f=0.40 (10% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−14.8 (*c*. 2.1, $CHCl_3$); ν_{max}, cm^{-1} (film) 3302, 2942, 2855, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.5 Hz), 6.87 (2H, d, *J*=8.5 Hz), 4.44 (1H, d, *J*=11.6 Hz), 4.41 (1H, d, *J*=11.6 Hz), 3.87–3.83 (1H, m), 3.80 (3H, s), 3.60–3.58 (1H, m), 3.54–3.51 (2H, m), 3.42–3.39 (1H, m), 2.44 (1H, ddd, *J*=16.6, 5.6, 2.6 Hz), 2.31 (1H, ddd, *J*=16.6, 7.7, 2.5 Hz) 2.01–2.08 (1H, m), 1.99 (1H, t, *J*=2.5 Hz), 1.88–1.85 (1H, m), 1.80–1.73 (2H, m), 1.27–1.20 (2H, m), 1.05 (21H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.1, 132.7, 131.3, 115.7, 82.8, 75.8, 74.7, 74.6, 71.9, 70.4, 68.2, 57.3, 43.8, 42.9, 38.1, 27.7, 20.1, 14.3; *m/z* (CI+) 478.5 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 478.3360, $[C_{27}H_{48}NO_4Si]^+$ requires 478.3353.

5.1.8. Alkyne 35. Prepared in 79% yield from alcohol **34** via the procedure described for **14**. R_f=0.40 (10% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−8.3 (*c*. 4.8, $CHCl_3$); ν_{max}, cm^{-1} (film) 3302, 2943, 2856, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 4.45 (1H, d, *J*=11.4 Hz), 4.43 (1H, d, *J*=11.4 Hz), 4.35–4.28 (1H, m), 4.05–3.98 (1H, m), 3.99–3.89 (1H, m), 3.80 (3H, s), 3.61–3.54 (2H, m), 2.42 (1H, dq, *J*=16.5, 5.4, 2.7 Hz), 2.31 (1H, ddd, *J*=16.5, 7.5, 2.5 Hz), 1.97 (1H, t, *J*=2.5 Hz), 1.84 (1H, br d, *J*=12.9 Hz), 1.81–1.73 (1H, m), 1.72–1.63 (2H, m), 1.46–1.34 (2H, m), 1.05 (21H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4, 129.2, 127.5, 112.0, 79.3, 70.9, 68.5, 68.1, 67.6, 65.0, 63.4, 53.6, 37.8, 36.9, 34.6, 24.2, 16.5, 10.6; *m/z* (CI+) 461 ($[M+H]^+$, 95%), 478.5 ($[M+NH_4]^+$, 40%); HRMS (ES+) Found 461.3082, $[C_{27}H_{45}O_4Si]^+$ requires 461.3087.

5.1.9. Ketone 15. To a stirred solution of alkyne **14** (1.38 g, 3.00 mmol) in THF (65 mL) was added sequentially pyridinium *p*-toluenesulfonate (414 mg, 4.50 mmol), H_2O (108 μL, 6.00 mmol) and mercury-(II)-acetate (300 mg, 0.90 mmol). After 1.5 h at 45°C, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (50 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography afforded ketone **15** (1.27 g, 86%) as a colourless oil; R_f=0.23 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−9.4 (*c*. 1.7, $CHCl_3$); ν_{max}, cm^{-1} (film) 2943, 2855, 1714, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.6 Hz), 6.87 (2H, d, *J*=8.6 Hz), 4.40 (2H, br s), 3.89–3.84 (1H, m), 3.80 (3H, s), 3.76–3.68 (1H, m), 3.54–3.45 (2H, m), 2.66 (1H, dd, *J*=15.4, 8.2 Hz), 2.40 (1H, dd, *J*=15.4, 4.5 Hz), 2.15 (3H, s), 1.91–1.85 (1H, m), 1.75–1.71 (2H, m), 1.24–1.17 (2H, m), 1.04 (21H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.3, 160.1, 131.7, 130.3, 114.8, 73.8, 73.6, 73.1, 69.4, 67.4, 56.3, 50.8, 42.8, 42.7, 37.2, 31.9, 19.1, 13.3; *m/z* (CI+) 496 ($[M+NH_4]^+$, 3%); HRMS (ES+) Found 479.3193, $[C_{27}H_{47}O_5Si]^+$ requires 479.3193.

5.1.10. Ketone 36. Prepared in 86% yield from **35** via the procedure described for **15**. R_f=0.23 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−13.2 (*c*. 6.2, $CHCl_3$); ν_{max}, cm^{-1} (film) 2943, 2855, 1714, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.85 (2H, d, *J*=8.6 Hz), 4.42 (2H, d, *J*=11.5 Hz), 4.39 (2H, d, *J*=11.5 Hz), 3.89–3.84 (1H, m), 3.80 (3H, s), 3.76–3.68 (1H, m), 4.27–4.22 (2H, m), 4.00–3.94 (1H, m), 3.52 (2H, br t, *J*=6.1 Hz), 2.56 (1H, dd, *J*=14.9, 8.3 Hz), 2.36 (1H, dd, *J*=14.9, 4.9 Hz), 2.14 (3H, s), 1.73–1.63 (4H, m), 1.42–1.36 (2H, m), 1.04 (21H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.6, 159.1, 130.8, 129.2, 113.7, 72.6, 69.2, 68.7, 66.7, 65.1, 55.3, 50.3, 39.4, 36.4, 30.6, 18.1, 17.7, 12.2; *m/z* (CI+) 479 ($[M+H]^+$, 80%), 496 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 479.3187, $[C_{27}H_{47}O_5Si]^+$ requires 479.3193.

5.1.11. Amide 18. To a cold (−78°C), stirred suspension of vacuum dried LiCl (7.20 g, 169 mmol) in THF (28 mL) was added diisopropylamine (8.90 mL, 63.5 mmol) followed by *n*-butyl lithium (29.6 mL, 59.3 mmol, 2 M in hexanes). After warming to 0°C and stirring for 10 min, the reaction mixture was cooled to −78°C, then treated with a solution of (*R*,*R*)-*N*-(2-hydroxy-1-methyl-2-phenethyl)-*N*-methylpropionamide (**16**)[15] (6.24 g, 28.2 mmol) in THF (70 mL) and stirred for a further 1 h. The reaction mixture was then warmed to 0°C for 15 min, and then to room temperature for 5 min. The mixture was cooled to 0°C, then treated with a solution of iodide **17** (16.9 g, 56.5 mmol) in THF (30 mL). After 1.5 h, the reaction mixture was cannulated into a pre-cooled (0°C) mixture of sat. aqueous NH_4Cl (100 mL), MeOH (50 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (50% EtOAc/40–60 petroleum ether) afforded the amide **18** (9.56 g, 86%; ≥40:1 dr) as a colourless oil; R_f=0.55 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−101.8 (*c*. 0.55, $CHCl_3$); ν_{max}, cm^{-1} (film) 3378, 2932, 2844, 1616; ^1H NMR (500 MHz, DMSO-*d*6, 120°C) δ 7.37 (2H, br d, *J*=7.1 Hz), 7.31 (2H, br t, *J*=7.4 Hz), 7.24 (1H, br t, *J*=7.1 Hz), 4.90 (1H, m), 4.60 (1H, m), 3.58 (2H, td, *J*=6.5, 0.9 Hz), 2.95 (3H, s), 2.73–2.70 (1H, m), 1.45–1.40 (1H, m), 1.46–1.39 (2H, m), 1.37–1.29 (1H, m), 1.00 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.7 Hz), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz, DMSO-*d*6, 120°C) δ 175.5, 142.9, 127.2, 126.4, 126.1, 73.9, 64.1, 62.3, 39.1, 34.3, 29.6, 29.5, 25.2, 17.3, 16.8, 14.3, −5.9, −5.9; *m/z* (ES+) 394 ($[M+H]^+$, 8%), 416 ($[M+Na]^+$, 100%); HRMS (ES+) Found 416.2616, $[C_{22}H_{39}NO_3SiNa]^+$ requires 416.2597.

5.1.12. Alcohol 19. To a cold (−78°C), stirred solution of diisopropylamine (14.0 mL, 100 mmol) in THF (90 mL) was added *n*-butyl lithium (99.3 mL, 97.1 mmol, 2 M in hexanes). After warming to 0°C for 15 min, the mixture was treated with $BH_3{\cdot}NH_3$ (2.94 g, 95.6 mmol) and stirred for an additional 15 min. The reaction mixture was then warmed to room temperature, stirred for 15 min, re-cooled to 0°C, and treated with a solution of amide **18** (9.40 g, 23.9 mmol). Stirring was continued for 2 h then the reaction mixture was cannulated into a pre-cooled (0°C) mixture of sat. aqueous NH_4Cl (100 mL), MeOH (50 mL) and Et_2O (50 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine. dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (20% Et_2O/30–40 petroleum ether) afforded alcohol **19** (5.53 g, 99%) as a colourless oil; R_f=0.65 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−10.3 (*c*. 1.15, $CHCl_3$); ν_{max}, cm^{-1} (film) 3378, 2932, 2844, 1616; 3357, 2932, 2856; ^1H NMR (400 MHz, $CDCl_3$) δ 3.58 (2H, br t, *J*=6.5 Hz), 3.47 (1H, dd, *J*=10.5, 5.9 Hz), 3.40 (1H, dd, *J*=10.5, 6.4 Hz), 1.71 (1H, br s), 1.65–1.34 (4H, m), 1.18–1.10 (1H, m), 0.90 (3H, d, *J*=6.7 Hz,), 0.86 (9H, s), 0.03 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 70.2, 65.6, 37.6, 32.9, 32.2, 31.3, 28.0, 20.4, 18.7, −3.3; *m/z* (ES+) 255 ($[M+Na]^+$, 25%); HRMS (ES+) Found 255.1757, $[C_{12}H_{28}O_2SiNa]^+$ requires 255.1756.

5.1.13. Aldehyde 5. To a stirred solution of alcohol **19** (2.20 g, 9.48 mmol) in CH_2Cl_2 (35 mL) was added Dess–Martin periodinane (5.20 g, 12.3 mmol). After 1.5 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (50 mL) and sat. aqueous $Na_2S_2O_3$ (50 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (15% Et_2O/40–60 petroleum ether) gave the aldehyde **5** (1.85 g, 85%), as a colourless oil, which was used directly in the next step to avoid any racemisation; R_f=0.3 (10% Et_2O/30–40 petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, d, *J*=1.9 Hz), 3.61 (1H, br t, *J*=6.2 Hz), 2.39–2.31 (1H, m), 1.80–1.70 (1H, m), 1.61–1.50 (2H, m), 1.47–1.36 (1H, m), 1.10 (3H, d, *J*=7.0 Hz), 0.88 (9H, s), 0.03 (6H, s).

5.1.14. Aldol adduct 21. To a cold (0°C), stirred solution of ketone **15** (200 mg, 0.42 mmol) in Et_2O (5 mL), was added sequentially Et_3N (94 μL, 0.67 mmol) and *c*-Hex_2BCl (158 μL, 0.57 mmol). After 30 min, the reaction mixture was cooled to −78°C and treated with a solution of freshly prepared aldehyde **5** (141 mg, 0.61 mmol) in Et_2O (2 mL). After 2 h, the mixture was warmed to −30°C, and maintained at this temperature for 18 h. Following warming

to 0°C, the reaction mixture was treated sequentially with pH 7 buffer (1.5 mL), MeOH (1.5 μL), and hydrogen peroxide (550 μL). After 1 h, brine (3 mL) was added, the organic phase separated, and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (20% Et_2O/30–40 petroleum ether) afforded aldol adduct **21** (300 mg, 99%; 17:1 dr) as a colourless oil; R_f=0.34 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+0.3 (*c*. 0.7, $CHCl_3$); ν_{max}, cm^{-1} (film) 3445, 2928, 2856, 1725, 1613; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.4 Hz), 6.86 (2H, d, *J*=8.4 Hz), 4.39 (2H, br s), 3.89–3.85 (2H, m), 3.79 (3H, s), 3.80–3.76 (1H, m), 3.60–3.57 (3H, m), 3.51–3.45 (3H, m), 3.07 (1H, br s), 2.72 (1H, dd, *J*=17.9, 9.3 Hz), 2.62 (1H, br dd, *J*=15.2 Hz), 2.51 (1H, dd, *J*=17.2, 9.7 Hz), 2.41 (1H, dd, *J*=15.0, 4.0 Hz), 1.91–1.86 (2H, m), 1.81–1.68 (2H, m), 1.61–1.40 (4H, m), 1.27–1.16 (3H, m), 1.04 (21H, m), 0.86–0.84 (12H, m), 0.04 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.7, 159.4, 130.6, 129.2, 124.1, 113.8, 72.7, 72.7, 72.0, 68.4, 68.3, 66.3, 55.2, 49.5, 47.2, 41.8, 37.9, 36.2, 30.9, 30.4, 28.4, 25.9, 18.3, 18.1, 15.1, 12.3, −5.3, −5.3; *m/z* (ES+) 726 ($[M+NH_4]^+$, 20%), 731 ($[M+Na]^+$, 100%); HRMS (ES+) Found 731.4714, $[C_{39}H_{72}O_7Si_2Na]^+$ requires 731.4714.

5.1.15. Aldol adduct 37. Prepared in 86% yield from **36** via the procedure described for **21**. R_f=0.34 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−2.8 (*c*. 2.15, $CHCl_3$); ν_{max}, cm^{-1} (film) 3466, 2943, 2866, 1709, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J*=8.6 Hz), 6.85 (2H, d, *J*=8.6 Hz), 4.40 (1H, d, *J*=11.5 Hz), 4.36 (1H, d, *J*=11.5 Hz), 3.89–3.85 (2H, m), 3.79 (3H, s), 3.80–3.76 (1H, m), 4.31–4.22 (2H, m), 3.98–3.90 (1H, m), 3.86–3.89 (1H, m), 3.57 (2H, br td, *J*=6.5, 1.9 Hz), 3.49 (2H, br t, *J*=6.1 Hz), 3.15 (1H, d, *J*=3.2 Hz), 2.69–2.57 (2H, m), 2.50 (1H, dd, *J*=17.3, 9.7 Hz), 2.36 (1H, dd, *J*=14.6, 4.7 Hz), 2.51 (1H, dd, *J*=17.2, 9.7 Hz), 2.41 (1H, dd, *J*=15.0, 4.0 Hz), 1.91–1.86 (2H, m), 1.74–1.36 (11H, m), 1.04 (21H, m), 0.88 (9H, s), 0.87 (3H, d, *J*=6.8 Hz), 0.04 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.5, 158.5, 130.2, 128.6, 113.2, 72.1, 70.6, 68.8, 68.3, 66.1, 64.4, 62.9, 54.6, 49.3, 46.5, 38.8, 37.3, 35.7, 35.0, 29.8, 27.8, 25.4, 23.5, 17.5, 14.5, 11.7, −5.8; *m/z* (ES+) 709 ($[M+H]^+$, 80%), 726 ($[M+NH_4]^+$, 50%); HRMS (ES+) Found 709.4900, $[C_{39}H_{73}O_7Si_2]^+$ requires 709.4895.

5.1.16. Diol 22. To a stirred suspension of tetramethylammonium triacetoxyborohydride (3.28 g, 12.5 mmol) in MeCN (39 mL) was added AcOH (13 mL). After 1 h, the mixture was cooled to −35°C and treated with a solution of ketone **21** (760 mg, 1.05 mmol) in MeCN (4 mL). After 28 h, the reaction mixture was warmed to −15°C and stirred for an additional 2 h then decanted into a mixture of sat. aqueous $NaHCO_3$ (20 mL), sat. aqueous sodium potassium tartrate (20 mL) and Et_2O (20 mL). After stirring for 30 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography afforded diol **22** (750 mg, 99%; ≥50:1 dr) as a colourless oil; R_f=0.20 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−1.6 (*c*. 0.55, $CHCl_3$); ν_{max}, cm^{-1} (film) 3448, 2937, 2857, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 4.41 (2H, br s), 4.22–4.13 (2H, m), 3.87–3.82 (1H, m), 3.80 (3H, s), 3.76–3.70 (1H, m), 3.64–3.55 (4H, m), 3.51–3.45 (3H, m), 3.15 (1H, br s), 1.88–1.78 (3H, m), 1.76–1.71 (1H, m), 1.64–1.59 (1H, m), 1.55–1.43 (7H), 1.36–1.25 (2H, m), 1.16–1.09 (1H, m), 1.05 (21H, m), 0.89 (9H, s), 0.87 (3H, d, *J*=7.1 Hz), 0.05 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.1, 129.4, 128.3, 112.7, 72.4, 71.7, 71.2, 69.5, 67.1, 65.3, 62.5, 54.2, 41.2, 41.1, 40.7, 37.9, 37.5, 34.9, 29.4, 27.4, 24.9, 17.3, 17.0, 16.7, 14.1, 11.3, −7.3, −7.3; *m/z* (ES+) 711 ($[M+H]^+$, 10%) 728 ($[M+NH_4]^+$, 20%), 733 ($[M+Na]^+$, 100%); HRMS (ES+) Found 733.4862, $[C_{39}H_{74}O_7Si_2Na]^+$ requires 733.4871.

5.1.17. Diol 38. Prepared in 86% yield from **37** via the procedure described for **22**. R_f=0.20 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−4.8 (*c*. 2.3, $CHCl_3$); ν_{max}, cm^{-1} (film) 3440, 2941, 1613; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 4.43 (1H, d, *J*=11.6 Hz), 4.39 (1H, d, *J*=11.6 Hz), 4.29–4.24 (2H, m), 4.24–4.16 (1H, m), 4.11 (1H, br t, *J*=10.9 Hz), 4.08–4.00 (1H, m), 3.80 (3H, s), 3.75 (1H, br t, *J*=7.5 Hz), 3.63–3.58 (2H, m), 3.50 (2H, br t, *J*=6.2 Hz), 3.35 (1H, br s), 1.77–1.72 (2H, m), 1.70–1.41 (13H, m), 1.04 (21H, m), 0.88–0.86 (12H, m), 0.04 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.5, 130.9, 129.7, 114.1, 73.9, 73.0, 72.6, 71.1, 70.2, 66.2, 65.1, 64.0, 55.6, 42.4, 40.4, 39.7, 39.1, 38.9, 36.5, 30.9, 28.8, 26.4, 18.5, 18.1, 15.5, 12.9, −4.9, −4.9; *m/z* (ES+) 711 ($[M+H]^+$, 95%); HRMS (ES+) Found 711.5048, $[C_{39}H_{75}O_7Si_2]^+$ requires 711.5051.

5.1.18. Triol 23. To a stirred solution of diol **22** (197 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (1.5 mL) was added 10-camphorsulfonic acid (6.0 mg, 0.027 mmol). After 3 h, the reaction mixture was treated with Et_3N (40 μL, 0.30 mmol) and concentrated in vacuo. Flash chromatography (Et_2O) afforded triol **23** (139 mg, 86%) as a colourless oil; R_f=0.20 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−2.1 (*c*. 0.80, $CHCl_3$); ν_{max}, cm^{-1} (film) 3389, 2942, 2856, 1610; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.6 Hz), 6.87 (2H, d, *J*=8.6 Hz), 4.42 (2H, br s), 4.22 (1H, br s), 4.19–4.13 (1H, m), 3.89–3.82 (1H, m), 3.80 (3H, s), 3.76–3.70 (1H, m), 3.66–3.60 (2H, br t, *J*=5.9 Hz), 3.58–3.42 (4H, m), 3.39 (1H, br s), 1.91–1.72 (5H, m), 1.69–1.47 (7H, m), 1.36–1.18 (3H, m), 1.05 (21H, m), 0.87 (3H, d, *J*=6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.1, 130.4, 129.3, 113.7, 77.2, 73.4, 72.7, 72.5, 70.5, 68.1, 66.4, 63.1, 55.3, 42.3, 42.1, 41.7, 39.1, 38.4, 36.0, 30.2, 28.4, 18.0, 15.3, 12.3; *m/z* (CI+) 597 ($[M+H]^+$, 100%); HRMS (ES+) Found 597.4187, $[C_{33}H_{61}O_7Si]^+$ requires 597.4186.

5.1.19. Triol from 38. To a stirred solution of diol **38** (1.56 g, 2.15 mmol) in CH_2Cl_2 (30 mL) and MeOH (1.3 mL) was added HCl (129 μL, 0.129 mmol, 1 M in Et_2O). After 3 h, the reaction mixture was treated with Et_3N (80 μL, 0.60 mmol) and concentrated in vacuo. Flash chromatography (Et_2O) afforded the corresponding triol (1.24 g, 94%) as a colourless oil; R_f=0.20 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=−5.3 (*c*. 1.7, $CHCl_3$); ν_{max}, cm^{-1} (film) 3411, 2942, 2856, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 4.43 (2H, d, *J*=11.3 Hz), 4.38 (1H, d, *J*=11.3 Hz), 4.27–4.19 (2H, m), 4.10 (1H, br t, *J*=10.9 Hz), 3.80 (3H, s), 3.75–3.68 (1H, m), 3.63 (2H, br

t, J=6.1 Hz), 3.51–3.47 (3H, m), 1.81 (1H, br s), 1.75 (1H, br ddd, J=13.1, 8.6, 2.3 Hz), 1.70–1.48 (11H, m), 1.24–1.17 (1H, m), 1.05 (21H, m), 0.87 (3H, d, J=6.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.5, 128.9, 127.7, 112.1, 72.0, 71.0, 70.8, 69.2, 68.3, 65.2, 63.2, 61.5, 53.6, 40.5, 38.4, 37.8, 37.4, 36.8, 34.6, 28.6, 26.8, 16.5, 13.7, 10.6; *m/z* (CI+) 597 ([M+H]$^+$, 40%); HRMS (ES+) Found 597.4187, $[C_{33}H_{61}O_7Si]^+$ requires 597.4186.

5.1.20. Lactone 24. To a stirred solution of triol **23** (545 mg, 0.91 mmol) in CH_2Cl_2 (16 mL) was added sequentially TEMPO (30 mg, 0.18 mmol) and iodobenzene diacetate (913 mg, 2.7 mmol). After 12 h, the reaction mixture was treated with 5% aqueous $Na_2S_2O_3$ (10 mL) and sat. aqueous $NaHCO_3$ (10 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (30% Et_2O/30–40 petroleum ether) afforded lactone **24** (497 mg, 92%) as a colourless oil; R_f=0.39 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+24.3 (*c*. 1.75, $CHCl_3$); ν_{max}, cm^{-1} (film) 3466, 2942, 2856, 1730, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, d, J=8.7 Hz), 6.85 (1H, d, J=8.7 Hz), 4.41 (1H, d, J=11.5 Hz), 4.37 (1H, d, J=11.5 Hz), 4.25 (1H, br td, J=10.7, 1.5 Hz), 4.22 (1H, br tt, J=9.9, 1.9 Hz), 3.87–3.80 (1H, m), 3.78 (3H, s), 3.57 (1H, br tt, J=9.6, 2.2 Hz), 3.52–3.49 (1H, m), 3.49 (2H, br t, J=6.4 Hz), 2.61 (1H, ddd, J=17.7, 6.9, 5.1 Hz), 2.61 (1H, ddd, J=17.6, 8.9, 6.9 Hz), 1.94–1.84 (1H, m), 1.89–1.68 (5H, m), 1.68–1.45 (6H, m), 1.31–1.19 (2H, m), 1.05 (21H, m), 0.87 (3H, d, J=6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4, 157.7, 129.1, 128.1, 112.4, 80.6, 75.6, 72.1, 71.4, 66.7, 66.0, 65.3, 53.9, 41.7, 40.9, 40.6, 40.4, 34.7, 31.5, 28.9, 26.3, 16.7, 16.0, 10.9; *m/z* (ES+) 610 ([M+NH$_3$]$^+$, 20%), 615 ([M+Na]$^+$, 100%); HRMS (ES+) Found 610.4131, $[C_{33}H_{60}NO_7Si]^+$ requires 610.4139.

5.1.21. Lactone 39. Prepared in 96% yield from the triol obtained from **38** via the procedure described for **24**. R_f=0.39 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$ +20.3 (*c*. 7.85, $CHCl_3$); ν_{max}, cm^{-1} (film) 3466, 2953, 2866, 1730, 1610, 1245; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, d, J=8.6 Hz), 6.85 (1H, d, J=8.6 Hz), 4.40 (2H, br s), 4.28–4.21 (3H, m), 4.13 (1H, br t, J=11.0 Hz), 4.05–3.97 (1H, m), 3.78 (3H, s), 3.50 (2H, br t, J=6.3 Hz), 2.59 (1H, ddd, J=17.7, 6.8, 5.1 Hz), 2.46 (1H, ddd, J=17.7, 9.1, 7.2 Hz), 1.88–1.85 (1H, m), 1.83–1.71 (2H, m), 1.68–1.61 (3H, m), 1.58–1.49 (4H, m), 1.46–1.34 (3H, m), 1.03 (21H, m), 0.99 (3H, d, J=6.5 Hz); ^{13}C NMR (62.5 MHz, CDCl3) δ 171.9, 159.1, 130.6, 129.3, 113.7, 82.0, 73.5, 72.7, 70.0, 67.5, 67.1, 64.8, 55.3, 43.1, 42.0, 40.0, 39.4, 36.3, 32.9, 29.4, 27.7, 18.1, 17.5, 12.2; *m/z* (ES+) 593 ([M+H]$^+$, 60%), 610 ([M+NH$_3$]$^+$, 20%), 615 ([M+Na]$^+$, 100%); HRMS (ES+) Found 593.3877, $[C_{33}H_{61}O_7Si]^+$ requires 593.3873.

5.1.22. Methyl ether 25. To a cold (0°C), stirred solution of lactone **24** (497 mg, 0.84 mmol) and Proton-Sponge® (1.79 g, 8.40 mmol) in CH_2Cl_2 (10 mL) was added trimethyloxonium tretafluoroborate (1.24 g, 8.40 mmol). After 2 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (20 mL), the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with 10% aqueous citric acid followed by brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (20% Et_2O/30–40 petroleum ether) afforded methyl ether **25** (429 mg, 84%) as a colourless oil; R_f=0.52 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+28.3 (*c*. 4.13, $CHCl_3$); ν_{max}, cm^{-1} (film) 3466, 2932, 2866, 1735, 1610, 1245; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, d, J=8.7 Hz), 6.86 (1H, d, J=8.7 Hz), 4.44 (1H, d, J=11.6 Hz), 4.40 (1H, d, J=11.6 Hz), 4.25 (1H, br t, J=9.2 Hz), 3.86–3.79 (1H, m), 3.79 (3H, s), 3.77–3.74 (1H, m), 3.60–3.54 (2H, m), 3.45–3.31 (2H, m), 3.31 (3H, s), 2.59 (1H, br dt, J=17.6, 4.7 Hz), 2.41 (1H, br dt, J=17.6, 7.1 Hz), 1.87–1.70 (7H, m), 1.65–1.51 (4H, m), 1.29–1.19 (2H, m), 1.05 (21H, m), 0.98 (3H, d, J=6.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.8, 159.7, 131.1, 129.4, 114.0, 82.4, 73.8, 72.8, 72.7, 72.1, 68.9, 66.9, 57.4, 55.5, 43.9, 43.2, 40.2, 39.0, 36.6, 33.2, 29.8, 28.1, 18.3, 17.8, 12.6; *m/z* (ES+) 624 ([M+NH$_3$]$^+$, 20%), 629 ([M+Na]$^+$, 100%); HRMS (ES+) Found 624.4287, $[C_{34}H_{62}NO_7Si]^+$ requires 624.4296.

5.1.23. Methyl ether 40. Prepared in 83% yield from lactone **39** via the procedure described for **25**. R_f=0.52 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+25.6 (*c*. 8.0, $CHCl_3$); ν_{max}, cm^{-1} (film) 2939, 2863, 1734, 1608, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, d, J=8.7 Hz), 6.86 (1H, d, J=8.7 Hz), 4.43 (2H, br s), 4.33–4.23 (1H, br t, J=9.3 Hz), 4.04–3.87 (2H, m), 3.78 (3H, s), 3.74 (1H, br dd, J=6.1 Hz), 3.58 (2H, br t, J=6.8 Hz), 2.57 (1H, br dt, J=17.8, 6.4 Hz), 2.39 (1H, br dt, J=17.6, 9.0 Hz), 1.93–1.33 (12H, m), 1.05 (21H, m), 0.96 (3H, d, J=5.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.0, 159.4, 131.4, 129.4, 114.1, 82.6, 73.8, 72.8, 69.4, 68.4, 67.4, 65.7, 65.6, 57.3, 55.6, 40.5, 40.3, 40.1, 40.0, 36.8, 33.3, 29.8, 28.1, 18.5, 12.6; *m/z* (CI+) 624 ([M+NH$_3$]$^+$, 90%), 607 ([M+H]$^+$, 35%); HRMS (ES+) Found 607.4027, $[C_{34}H_{59}NO_7Si]^+$ requires 607.4030.

5.1.24. Silyl enol ether 6.[23] To a cold (−78°C), stirred solution of 6-methyl-hept-3-en-2-one (3.00 g, 23.8 mmol) in THF (100 mL) was added sequentially TMSCl/Et_3N solution[§] (2.1 mL, 7.40 mmol) and lithium hexamethyldisilazide (4.9 mL, 4.9 mmol, 1 M in THF). After 10 min, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (100 mL), the organic phase separated and the aqueous phase extracted with 30–40 petroleum ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by distillation in vacuo (50–52°C, 0.5 mmHg) afforded silyl enol ether **6** as a colourless oil (3.9 g, 96%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.99–5.82 (2H, m), 4.23 (2H, br s), 1.98 (2H, t, J=6.4 Hz), 1.72–1.61 (1H, m), 0.89 (6H, d, J=6.6 Hz), 0.19 (9H, s).

5.1.25. Enone 27. To a cold (−78°C), stirred solution of methyl ether **25** (100 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) was added DIBAL (192 μL, 0.19 mmol, 1 M in CH_2Cl_2). After 2 h, the reaction mixture was treated sequentially with a solution of pyridine (242 μL, 1.80 mmol) and DMAP (120 mg, 0.96 mmol) in CH_2Cl_2 (1 mL) followed by Ac_2O (138 μL, 1.48 mmol). The reaction mixture was gradually warmed to −35°C over 12 h then filtered through a plug of

[§] Equal volumes of Et_3N and TMSCl were combined and the mixture centrifuged. The resulting supernatant liquid was taken to be ca. 3.5 M.

dry alumina (eluting with 40% Et_2O/30–40 petroleum ether) and concentrated in vacuo to give the intermediate acetate **26**. After azeotroping with toluene (3 x 2 mL), the acetate **26** was dried under high vacuum for 3 h prior to being used in the next step. To a cold (0°C), stirred solution of acetate **26** and silyl enol ether **6** (78 μL, 0.46 mmol) in CH_2Cl_2 was added dry $ZnBr_2$ (8.0 mg, 0.04 mmol). After 0.5 h, the reaction mixture was warmed to 5°C and treated with an additional quantity of **6** (78 μL, 0.46 mmol) followed by $ZnBr_2$ (8.0 mg, 0.04 mmol). After 3 h, the mixture was filtered and the filtrate concentrated in vacuo. Flash chromatography (gradient elution 10–20% Et_2O/30–40 petroleum ether) afforded enone **27** (96 mg, 81%) as a colourless oil; R_f=0.41 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+8.6 (*c*. 2.9, $CHCl_3$); ν_{max}, cm^{-1} (film) 2943, 2857, 1698, 1616, 1240; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J*=8.5 Hz), 6.86 (2H, d, *J*=8.5 Hz), 6.81 (1H, br tt, *J*=15.5, 7.5 Hz), 6.10 (1H, br d, 15.8 Hz), 4.44 (1H, d, *J*=11.4 Hz), 4.39 (1H, d, *J*=11.4 Hz), 4.35–4.26 (1H, m), 3.91–3.81 (1H, m), 3.79 (3H, s), 3.61–3.53 (3H, m), 3.52–3.47 (1H, m), 3.46–3.40 (1H, m), 3.39–3.34 (1H, m), 3.29 (3H, s), 2.87 (1H, dd, *J*=15.4, 6.3 Hz), 2.74 (1H, dd, *J*=15.4, 7.0 Hz), 2.09 (2H, br t, *J*=7.0 Hz), 1.90–1.84 (2H, m), 1.83–1.72 (4H, m), 1.72–1.62 (4H), 1.55–1.47 (2H, m), 1.40–1.33 (2H, m), 1.27–1.18 (2H, m), 1.05 (21H, m), 0.94–0.91 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3, 159.1, 146.5, 131.7, 130.8, 129.2, 113.8, 74.4, 73.1, 72.7, 72.4, 72.2, 68.8, 67.7, 66.8, 56.8, 55.2, 43.3, 42.6, 42.0, 41.7, 40.2, 38.3, 36.3, 33.9, 27.9, 27.7, 26.6, 22.4, 22.4, 18.3, 18.1, 12.3; *m/z* (ES+) 734 ($[M+NH_4]^+$, 5%), 739 ($[M+Na]^+$, 100%); HRMS (ES+) Found 734.5386, $[C_{42}H_{76}NO_7Si]^+$ requires 734.5391.

5.1.26. Enone 41. Prepared in 81% yield from lactone **40** via the procedures described for **27**. R_f=0.41 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+7.7 (*c*. 3.1, $CHCl_3$); ν_{max}, cm^{-1} (film) 2938, 2868, 1682, 1611, 1244; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J*=8.7 Hz), 6.86 (2H, d, *J*=8.7 Hz), 6.81 (1H, br tt, *J*=15.8, 7.6 Hz), 6.09 (1H, dt, 15.8, 1.2 Hz), 4.41 (2H, s), 4.33–4.25 (2H, m), 4.00–3.89 (2H, m), 3.79 (3H, s), 3.63–3.54 (2H, m), 3.54–3.45 (2H, m), 3.27 (3H, s), 2.87 (1H, dd, *J*=15.4, 6.4 Hz), 2.72 (1H, dd, *J*=15.5, 6.9 Hz), 2.08 (2H, br dd, *J*=6.9, 1.3 Hz), 1.82–1.58 (10H, m), 1.55–1.45 (2H, m), 1.45–1.26 (4H, m), 1.04 (21H, m), 0.96–0.88 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3, 158.9, 146.5, 131.7, 130.8, 129.1, 113.7, 74.3, 73.1, 72.6, 69.1, 68.4, 67.7, 67.3, 65.4, 56.9, 55.2, 43.3, 41.7, 40.3, 40.0, 39.7, 38.3, 36.5, 33.9, 27.9, 27.7, 26.6, 22.4, 22.3, 18.3, 18.1, 12.2; *m/z* (*EI*+) 716 ([M+], 90%), (CI+) 717 ($[M+H]^+$, 60%), 734 ($[M+NH_4]^+$, 80%); HRMS (ES+) Found 717.5121, $[C_{42}H_{73}O_7Si]^+$ requires 717.5125.

5.1.27. Alcohol 28. To a cold (−78°C), stirred solution of enone **27** (100 mg, 0.14 mmol) in CH_2Cl_2 (4 mL), was added $LiAlH(O\textit{t}\text{-}Bu)_3$(536 μL, 0.54 mmol, 1 M in THF). After warming to −10°C and stirring for 3 h, the reaction mixture was treated with 1N tartaric acid (2 mL), the organic phase separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (20% Et_2O/30–40 petroleum ether) afforded alcohol **28** (76 mg, 76%) as a colourless oil; R_f=0.25 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+12.2 (*c*. 3.6, $CHCl_3$); ν_{max}, cm^{-1} (film) 3444, 2942, 2856, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.5 Hz), 6.86 (2H, d, *J*=8.5 Hz), 5.63 (1H, br dt, *J*=15.0, 7.1 Hz), 5.44 (1H, dd, *J*=15.2, 6.5 Hz), 4.44 (1H, d, *J*=11.4 Hz), 4.38 (1H, d, *J*=11.4 Hz), 4.26–4.23 (1H, m), 3.95–3.87 (1H, m), 3.86–3.82 (1H, m), 3.79 (3H, s), 3.64–3.59 (1H, m), 3.58–3.53 (4H m), 3.49–3.38 (2H, m), 3.33, (3H, s), 1.93–1.85 (6H, m), 1.79–1.65 (4H, m), 1.62–1.51 (5H, m), 1.44–1.34 (3H, m), 1.31–1.17 (2H, m), 1.04 (21H, m), 0.99 (3H, d, *J*=6.5 Hz), 0.87 (3H, br d, *J*=6.3 Hz), 0.86 (3H, br d, *J*=5.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.3, 133.1, 129.9, 128.9, 128.5, 113.0, 76.5, 73.5, 72.3, 71.9, 71.7, 71.6, 71.4, 70.3, 67.9, 65.9, 55.7, 54.5, 41.7, 41.2, 40.8, 40.1, 38.8, 36.7, 35.6, 32.5, 27.5, 25.2, 21.6, 21.5, 17.7, 17.3, 11.6; *m/z* (ES+) 736 ($[M+NH_4]^+$, 20%), 741 ($[M+Na]^+$, 90%); HRMS (ES+) Found 736.5546, $[C_{42}H_{76}NO_7Si]^+$ requires 736.5548.

5.1.28. Alcohol from 41. Prepared in 89% yield from enone **41** via the procedure described for **28**. R_f=0.23 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+9.1 (*c*. 3.8, $CHCl_3$); ν_{max}, cm^{-1} (film) 3477, 2940, 2865, 1610, 1247; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J*=8.5 Hz), 6.85 (2H, d, *J*=8.5 Hz), 5.63 (1H, br dt, *J*=15.3, 7.1 Hz), 5.44 (1H, dd, *J*=15.3, 6.4 Hz), 4.40 (1H, s), 4.28–4.21 (2H, m), 3.99–3.87 (3H, m), 3.79 (3H, s), 3.74–3.66 (2H, m), 3.58–3.55 (3H, m), 3.31, (3H, s), 1.98–1.83 (3H, m), 1.83–1.72 (2H, m), 1.72–1.30 (15H, m), 1.04 (21H, m), 0.98 (3H, d, *J*=6.5 Hz), 0.87 (3H, br d, *J*=6.6 Hz), 0.86 (3H, br d, *J*=6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.0, 133.9, 130.8, 129.5, 129.1, 113.7, 74.4, 73.1, 72.6, 72.5, 71.1, 69.2, 68.4, 67.1, 65.3, 56.4, 55.2, 41.6, 41.2, 40.1, 39.7, 39.5, 37.1, 36.4, 33.1, 28.2, 28.1, 22.4, 22.3, 18.4, 18.1, 17.7, 12.2; *m/z* (ES+) 719 ($[M+H]^+$, 20%), 736 ($[M+NH_4]^+$, 80%); HRMS (ES+) Found 736.5546, $[C_{42}H_{76}NO_7Si]^+$ requires 736.5548.

5.1.29. Acetate from 28. To a cold (0°C), stirred solution of alcohol **28** (70 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added sequentially pyridine (40 μL, 0.50 mmol), DMAP (47 mg, 0.40 mmol) and Ac_2O (37 μL, 0.4 mmol). After 24 h, the reaction mixture was treated with sat. aqueous NH_4Cl (3 mL), the organic phase separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (20% Et_2O/30–40 petroleum ether) afforded the corresponding acetate (74 mg, 100%) as a colourless oil; R_f=0.36 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+11.0 (*c*. 0.4, $CHCl_3$); ν_{max}, cm^{-1} (film) 2932, 2855, 1730, 1610, 1245; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.7 Hz), 6.85 (2H, d, *J*=8.7 Hz), 5.72 (1H, br dt, *J*=15.0, 7.3 Hz), 5.35 (1H, dd, *J*=15.3, 7.5 Hz), 5.25 (1H, br q, *J*=8.0 Hz), 4.43 (1H, d, *J*=11.3 Hz), 4.37 (1H, d, *J*=11.3 Hz), 3.86–3.80 (2H, m), 3.79 (3H, s), 3.64–3.51 (3H, m), 3.49–3.36 (4H m), 3.33, (3H, s), 2.18–2.10 (1H, m), 2.02 (3H, s), 1.91 (2H, br t, *J*=6.8 Hz), 1.88–1.55 (13H, m), 1.52–1.43 (1H, m), 1.35–1.26 (3H), 1.04 (21H, m), 0.89 (3H, d, *J*=6.0 Hz), 0.86 (3H, d, *J*=6.6 Hz, *H*-22), 0.85 (3H, d, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 159.1, 133.8, 130.7, 129.2, 129.1, 113.7, 74.4, 72.7, 72.7, 72.3, 72.1, 72.0, 68.7, 68.1, 66.8, 56.7, 55.2, 42.6, 42.0, 41.6, 39.9, 38.8, 36.4, 36.3,

34.9, 28.2, 28.0, 27.0, 22.3, 22.2, 21.3, 18.3, 18.0, 12.3; *m/z* (ES+) 778 ($[M+NH_4]^+$, 12%), 783 ($[M+Na]^+$, 100%); HRMS (ES+) Found 783.5215, $[C_{44}H_{76}O_8SiNa]^+$ requires 783.5207.

5.1.30. Acetate from 41. Prepared in ca. 100% yield from the reduction product of **41** via the procedure described for the acetate from **28**. R_f=0.36 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+10.3 (*c*. 3.3, $CHCl_3$); ν_{max}, cm^{-1} (film) 2932, 2855, 1735, 1610, 1240; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.5 Hz), 6.85 (2H, d, *J*=8.5 Hz), 5.72 (1H, br dt, *J*=15.0, 7.2 Hz), 5.36 (1H, br dd, *J*=15.3, 7.5 Hz), 5.25 (1H, br q, *J*=7.4 Hz), 4.42 (1H, d, *J*=11.7 Hz), 4.40 (1H, d, *J*=11.7 Hz), 4.31–4.22 (1H, m), 4.02–3.88 (2H, m), 3.86–3.81 (1H, m), 3.79 (3H, s), 3.63–3.52 (3H, m), 3.51–3.43 (1H, m), 3.32, (3H, s), 2.21–2.11 (1H, m), 2.00 (3H, s), 1.92 (2H, br t, *J*=7.0 Hz), 1.79–1.74 (2H, m), 1.73–1.35 (13H, m), 1.35–1.25 (1H, m), 1.04 (21H, m), 1.02–0.96 (1H, m), 0.89 (3H, d, *J*=5.9 Hz), 0.87 (3H, d, *J*=6.6 Hz), 0.85 (3H, d, *J*=6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 159.0, 134.2, 131.3, 129.6, 129.5, 114.1, 74.8, 73.1, 73.0, 72.7, 69.5, 68.7, 68.5, 67.1, 65.8, 57.0, 55.6, 42.0, 40.6, 40.5, 40.1, 39.1, 37.0, 36.9, 35.2, 28.5, 28.5, 27.4, 22.7, 22.6, 21.8, 18.7, 18.5, 12.6; *m/z* (CI+) 778 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 778.5653, $[C_{44}H_{80}NO_8Si]^+$ requires 778.5653.

5.1.31. Alcohol 29. To a stirred solution of the acetate of **28** (70 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) and pH 7 buffer (0.4 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (90 mg, 0.40 mmol). After 3 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (4 mL), the organic phase separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (2×5 mL), dried (Na_2CO_3), and concentrated in vacuo. Flash chromatography (30% Et_2O/30–40 petroleum ether) afforded the alcohol **29** (65 mg, 99%) which was taken on to the next step; R_f=0.11 (20% EtOAc/40–60 petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, br dt, *J*=14.8, 7.6 Hz), 5.33 (1H, br dd, *J*=15.3, 7.5 Hz), 5.25 (1H, br q, *J*=7.8 Hz), 3.89–3.81 (3H, m), 3.65–3.60 (2H, m), 3.54–3.47 (2H, m), 3.45–3.36 (1H, m), 3.36, (3H, s), 3.14 (1H, br s), 2.25–2.17 (1H, m), 2.00 (3H, s), 1.90–1.81 (4H, m), 1.71–1.58 (8H, m), 1.47–1.41 (3H, m), 1.32–1.25 (3H, m), 1.03 (21H, m), 0.87–0.84 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4, 134.5, 129.4, 75.0, 74.2, 73.3, 73.1, 72.6, 69.1, 69.0, 59.8, 57.0, 42.7, 42.4, 42.0, 39.7, 38.7, 38.1, 36.4, 35.7, 28.9, 28.4, 27.6, 22.7, 22.6, 21.7, 18.6, 18.5, 12.7.

5.1.32. Alcohol 42. Prepared in 98% yield from the corresponding PMB ether via the procedure described for **29**. R_f=0.11 (20% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+15.8 (*c*. 2.9, $CHCl_3$); ν_{max}, cm^{-1} (film) 3455, 2932, 2877, 1736; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, br dt, *J*=14.9, 7.2 Hz), 5.35 (1H, br dd, *J*=15.3, 7.5 Hz), 5.21 (1H, br q, *J*=7.7 Hz), 4.30–4.23 (1H, m), 4.09–3.91 (2H, m), 3.89–3.83 (1H, m), 3.83–3.73 (1H, m), 3.72–3.53 (2H, m), 3.51–3.41 (1H, m), 3.30, (3H, s), 3.19 (1H, br s), 2.22–2.13 (1H, m), 1.98 (3H, s), 1.88 (2H, br t, *J*=6.8 Hz), 1.85–1.77 (1H, m), 1.73–1.23 (17H, m), 1.03 (21H, m), 0.85–0.82 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.7, 135.7, 130.8, 76.3, 74.4, 73.9, 72.8, 70.7, 70.1, 66.9, 61.9, 58.3, 43.3, 41.6, 41.4, 40.5, 39.6, 37.8, 36.8, 30.1, 29.7, 29.5, 28.8, 24.0, 23.9, 23.1, 19.9, 19.8, 13.9; *m/z* (ES+) 641 ($[M+H]^+$, 70%), 658 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 641.4821, $[C_{36}H_{69}O_7Si]^+$ requires 641.4812.

5.1.33. Acid 30. To a stirred solution of the alcohol **29** (65 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added TEMPO (5 mg, 0.03 mmol) followed by iodobenzene diacetate (97 mg, 0.30 mmol). After 2 h, the reaction mixture was treated with 5% aqueous $Na_2S_2O_3$ (1 mL) and sat. aqueous $NaHCO_3$ (1 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was filtered through a plug of silica gel (eluting with 50% Et_2O) and the filtrate concentrated in vacuo to afford the corresponding aldehyde which was used directly in the next step. To a stirred solution of the intermediate aldehyde in *t*-BuOH (1 mL) was added methyl-2-butene (ca. 0.5 mL) in *t*-BuOH (0.5 mL). The reaction mixture was cooled (0°C) and treated with a solution of $NaClO_2$ (36 mg, 0.3 mmol) and NaH_2PO_4 (142 mg, 0.91 mmol) in H_2O (1 mL). After 1.5 h, the reaction mixture was diluted with brine (3 mL) and Et_2O (3 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Et_2O) afforded the acid **30** (56 mg, 85%) which was taken on to the next step; R_f=0.4 (50% EtOAc/40–60 petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (1H, br dt, *J*=15.0, 7.2 Hz), 5.35 (1H, dd, *J*=15.2, 7.6 Hz), 5.25 (1H, br q, *J*=8.1 Hz), 3.90–3.86 (2H, m), 3.75–3.71 (1H, m), 3.57–3.49 (1H, m), 3.48–3.39 (2H, m), 3.31 (3H, s), 2.52 (1H, dd, *J*=12.7, 3.7 Hz), 2.47 (1H, br d, *J*=12.7 Hz), 2.26–2.19 (1H, m), 2.03 (3H, s), 1.95 (2H, br t, *J*=6.8 Hz), 1.90–1.85 (3H, m), 1.81–1.69 (2H, m), 1.68–1.57 (2H, m), 1.57–1.49 (2H, m), 1.49–1.43 (2H, m), 1.38–1.22 (4H, m), 1.04 (21H, m), 0.88 (3H, d, *J*=6.3 Hz), 0.87 (6H, br d, 6.7 Hz).

5.1.34. Acid 43. Prepared in 98% yield from alcohol **42** via the procedure described for **30**; R_f=0.4 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+15.5 (*c*. 3.7, $CHCl_3$); ν_{max}, cm^{-1} (film) 3184, 2940, 2870, 1735, 1713; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (1H, br dt, *J*=15.0, 7.2 Hz), 5.37 (1H, br dd, *J*=15.3, 7.6 Hz), 5.25 (1H, br q, *J*=7.8 Hz), 4.34–4.28 (1H, m), 4.27–4.20 (1H, m), 4.09–3.97 (1H, m), 3.94–3.84 (1H, m), 3.52–3.45 (1H, m), 3.49–3.44 (1H, m), 3.31, (3H, s), 2.50 (1H, dd, *J*=15.3, 4.1 Hz), 2.43 (1H, dd, *J*=15.3, 8.9 Hz), 2.25–2.18 (1H, m), 2.02 (3H, s), 1.92 (2H, br t, *J*=7.0 Hz), 1.81–1.24 (15H, m), 1.02 (21H, m), 0.89 (3H, d, *J*=6.1 Hz), 0.87 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6, 170.1, 134.0, 128.8, 75.2, 72.9, 72.6, 69.8, 68.5, 68.3, 64.7, 56.4, 41.5, 41.0, 40.2, 39.5, 38.8, 38.4, 36.2, 34.8, 28.2, 27.9, 27.0, 22.2, 22.1, 21.3, 18.1, 17.9, 12.1; *m/z* (CI+) 672 ($[M+NH_4]^+$, 90%); HRMS (ES+) Found 672.4874, $[C_{36}H_{70}NO_8Si]^+$ requires 672.4871.

5.1.35. Macrolactone 31. To a stirred solution of acid **30** (56 mg, 85%) in MeOH (2 mL) was added K_2CO_3 (591 mg, 4.30 mmol). After 5 h, the reaction mixture was diluted with Et_2O (2 mL), filtered, and the filtrate concentrated in vacuo to give the crude product which was filtered through a small pad

of silica gel (eluting with 2% MeOH/Et_2O). Concentration of the filtrate in vacuo afforded the *seco*-acid which was azeotroped from toluene (3×2 mL) and used directly in the next step. To a stirred solution of triphenylphosphine (58 mg, 0.22 mmol) in degassed benzene (6 mL) was added sequentially diethylazodicarboxylate (29 μL, 0.184 mmol) and a solution of *seco*-acid (21 mg, 0.034 mmol) in degassed benzene (1.0 mL). After 15 min, the reaction mixture was concentrated in vacuo. Flash chromatography (15% Et_2O/30–40 petroleum ether) afforded macrolactone **31** (16 mg, 65%) as a colourless oil; R_f=0.65 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+57.2 (*c*. 0.8, $CHCl_3$); ν_{max}, cm^{-1} (film) 2942, 2866, 1741; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (1H, br dt, *J*=14.5, 7.2 Hz), 5.41–5.32 (2H, m), 3.98–3.85 (2H, m), 3.68 (1H, br t, *J*=11.3 Hz), 3.59–3.48 (2H, m), 3.36 (3H, s), 3.17 (1H, br t, *J*=11.1 Hz), 2.56 (1H, dd, *J*=14.6, 3.8 Hz), 2.42–2.35 (2H, m), 2.02 (1H, br td, 13.5, 2.0 Hz), 1.98–1.79 (6H, m), 1.69–1.56 (4H, m), 1.56–1.48 (2H, m), 1.48–1.40 (1H, m), 1.36–1.28 (2H, m), 1.22 (1H, br td, *J*=13.2, 1.9 Hz), 1.18 (3H, d, *J*=7.1 Hz), 1.07 (21H, m), 1.05–0.96 (1H, m), 0.88 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 132.3, 130.2, 73.7, 73.6, 73.0, 72.2, 70.7, 68.5, 62.9, 57.3, 43.2, 42.9, 41.8, 41.6, 39.3, 35.6, 31.1, 28.1, 27.2, 24.2, 22.2, 18.2, 18.1, 17.7, 12.3, 12.3; *m/z* (ES+) 595 ($[M+H]^+$, 30%), 612 ($[M+NH_4]^+$, 40%), 617 ($[M+Na]^+$, 60%); HRMS (ES+) Found 617.4234, $[C_{34}H_{62}O_6SiNa]^+$ requires 617.4213.

5.1.36. Macrolactone 44. Prepared in 48% yield from **43** via the procedure described for **31**. R_f=0.65 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+60.7 (*c*. 1.95, $CHCl_3$); ν_{max}, cm^{-1} (film) 2939, 2869, 1740; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (1H, br dt, *J*=15.0, 7.2 Hz), 5.38 (1H, br dd, *J*=15.2, 6.7 Hz), 5.31 (1H, br dd, *J*=11.1, 6.7 Hz), 4.38–4.31 (1H, m), 4.20 (1H, br t, *J*=11.1 Hz), 3.91–3.79 (2H, m), 3.58 (1H, br t, *J*=10.6 Hz), 3.52 (1H, br t, *J*=10.7 Hz), 3.35 (3H, s), 2.47 (1H, dd, *J*=13.0, 3.7 Hz), 2.41 (1H, br t, *J*=14.2 Hz), 2.29 (1H, br td, *J*=13.0), 1.95 (1H, br t, *J*=11.7 Hz), 1.94–1.78 (2H, m), 1.72–1.39 (11H, m), 1.33–1.25 (1H, m), 1.16 (3H, d, *J*=7.0 Hz), 1.14–0.95 (23H, m), 0.86 (6H, d, *J*=6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.9, 132.0, 130.0, 73.7, 73.6, 70.7, 69.4, 69.3, 65.5, 63.1, 57.3, 43.3, 43.1, 41.6, 41.6, 39.5, 39.3, 35.7, 30.9, 28.1, 27.2, 24.0, 22.3, 18.2, 18.1, 17.7, 17.2, 12.3; *m/z* (CI+) 595 ($[M+H]^+$, 30%), 612 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 595.4394, $[C_{34}H_{63}O_6SiN]^+$ requires 595.4394.

5.1.37. Alcohol 32. To a cold (0°C), stirred solution of macrolactone **31** (13 mg, 0.022 mmol) in THF (1.5 mL) was added HF·pyr (100 μL, 1.1 mmol). After 4 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (5 mL) and Et_2O (2 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (Et_2O) gave alcohol **32** (9.0 mg, 95%) as a colourless oil; R_f=0.1 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+56.0 (*c*. 0.1, EtOH); ν_{max}, cm^{-1} (film) 3433, 2932, 2866, 1730; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (1H, td, *J*=15.0, 7.2 Hz), 5.45–5.30 (2H, m), 3.94 (2H, m), 3.74 (1H, tq, *J*=11.3, 2.0 Hz), 3.54 (2H, m), 3.37 (3H, s), 3.23 (1H, br t, *J*=1.3 Hz), 2.58 (1H, dd, *J*=13.2, 3.9 Hz), 2.40 (1H, dd, *J*=13.2, 11.5 Hz), 2.38 (1H, br dd, *J*=14.0, 12.2 Hz), 2.07–2.01 (2H, m), 1.96–1.84 (4H, m), 1.78–1.57 (4H, m), 1.56–1.43 (4H, m), 1.35–1.21 (4H, m), 1.18 (3H, d, *J*=7.1 Hz), 1.05–0.98 (1H, m), 0.89 (3H, d, *J*=6.6 Hz), 0.87 (3H, d, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 132.3, 130.1, 73.6, 73.5, 73.0, 72.1, 70.8, 68.0, 63.0, 57.3, 43.1, 42.8, 41.6, 41.1, 40.8, 39.2, 35.5, 35.5, 31.0, 28.1, 27.1, 24.2, 22.2, 18.3; *m/z* (ES+) 439 ($[M+H]^+$, 5%), 456 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 456.3325, $[C_{25}H_{46}NO_6]^+$ requires 456.3325.

5.1.38. Alcohol 45. To a cold (0°C), stirred solution of macrolactone **44** (37 mg, 0.062 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (316 μL, 0.316 mmol, 1 M in THF). After 5 h, the reaction mixture was diluted with sat. aqueous NH_4Cl (3 mL) followed by Et_2O (3 mL). The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (60% Et_2O/30–40 petroleum ether) afforded alcohol **45** (27 mg, 99%) as a colourless amorphous solid. R_f=0.1 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+26.0 (*c*. 0.1, EtOH); ν_{max}, cm^{-1} (film) 3444, 2921, 2866, 1735; ^1H NMR (500 MHz, C_6D_5N) δ 6.37 (1H, d, *J*=3.1 Hz), 5.85 (2H, m), 5.59 (1H, ddt, *J*=15.4, 6.9, 1.3 Hz), 4.68 (1H, dddd, *J*=11.6, 3.7, 1.7 Hz), 4.46 (1H, m), 4.22 (1H, br dd, *J*=11.5 Hz), 4.10 (1H, br d, *J*=10.7 Hz), 3.97 (1H, br dd, *J*=10.0 Hz), 3.80 (1H, tt, *J*=11.0, 2.2 Hz), 3.41 (3H, s), 2.73 (1H, dd, *J*=13, 3.7 Hz), 2.53 (1H, br dd, *J*=11.9 Hz), 2.52 (1H, dd, *J*=13.1, 11.6 Hz), 2.15 (1H, br ddd, *J*=13.0, 11.5, 2.1 Hz), 1.96 (1H, br d, *J*=13.0 Hz), 1.93–1.86 (4H, m), 1.77 (1H, ddd, *J*=14.7, 10.5, 2.0 Hz), 1.67 (1H, br dddd, *J*=14.0, 13.2, 4.6 Hz), 1.65 (1H, br ddd, *J*=13.7, 11.3, 3.0 Hz), 1.51–1.55 (2H, m), 1.45–1.35 (3H, m), 1.27–1.21 (1H, m), 1.17–1.15 (1H, m), 1.12 (3H, d, *J*=7.0 Hz), 1.08 (1H, ddd, *J*=14.3, 12.0, 2.4 Hz), 0.83 (3H, d, *J*=6.6 Hz), 0.82 (3H, d, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 131.9, 131.5, 73.9, 73.9, 70.9, 69.8, 69.7, 63.8, 63.1, 56.7, 43.9, 43.4, 41.7, 40.0, 39.7, 39.5, 35.9, 31.4, 28.3, 27.4, 24.3, 22.3, 22.2, 18.4; *m/z* (ES+) 439 ($[M+H]^+$, 50%), 456 ($[M+NH_4]^+$, 95%); HRMS (ES+) Found 439.3057, $[C_{25}H_{43}O_6]^+$ requires 456.3059. This spectrocopic and specific rotation data was in agreement with that reported by Pietra[3] and Leighton.[6a]

5.1.39. Ketone 33. To a stirred solution of alcohol **32** or **45** (9.0 mg, 0.021 mmol) in CH_2Cl_2 (0.5 mL) was added sequentially pyridine (3 μL, 0.041 mmol) and Dess–Martin periodinane (17.0 mg, 0.041 mmol). After 1.5 h, the reaction mixture was filtered through a short column of silica gel (eluting with 50% Et_2O/30–40 petroleum ether) and the filtrate concentrated in vacuo. Flash chromatography afforded ketone **33** (9.0 mg, 99%) as a colourless glass; R_f=0.65 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+53.0 (*c*. 1.5, EtOH); ν_{max}, cm^{-1} (film) 2954, 2868, 1738, 1715; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75–5.66 (1H, m), 5.45–5.30 (2H, m), 4.02 (1H, tt, *J*=11.2, 2.6 Hz), 3.86 (1H, br dd, *J*=11.5, 11.5 Hz), 3.59–3.44 (3H, m), 3.37 (3H, s), 2.63 (1H, dd, *J*=13.2, 3.6 Hz), 2.51–2.40 (2H, m), 2.39–2.21 (4H, m), 2.09 (1H, br td, *J*=13.3, 1.4 Hz), 1.96–1.81 (2H, m), 1.76–1.55 (3H, m), 1.53–1.44 (3H, m), 1.41 (1H, br d, *J*=10.7 Hz), 1.32–1.28 (2H, m), 1.15 (3H, d,

J=7.1 Hz), 1.04 (1H, br tt, J=12.6, 1.3 Hz), 0.84 (1H, d, J=6.6 Hz), 0.83 (1H, d, J=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 168.5, 132.8, 129.8, 74.3, 73.5, 73.4, 71.2, 63.1, 57.3, 63.0, 47.9, 47.4, 43.4, 42.7, 41.5, 39.6, 39.0, 35.6, 31.0, 28.1, 27.1, 24.2, 22.2, 18.3; m/z (ES+) 437 ($[M+H]^+$, 5%), 454 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 437.2905, $[C_{25}H_{41}O_6]^+$ requires 437.2903.

5.1.40. Alcohol 32. To a cold (−100°C), stirred solution of ketone **33** (26 mg, 0.06 mmol), in THF (100 mL), was added L-Selectride® (90 μL, 0.09 mmol, 1 M in THF). After 1.5 h, the reaction mixture was treated with sat. aqueous NH_4Cl (2 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (70% Et_2O/30–40 petroleum ether) afforded alcohol **32** as a colourless oil (24 mg, 91%) with data as already listed (5.1.37).

5.1.41. Ketone 47. To a cold (−78°C), stirred solution of diisopropylamine (8.50 mL, 62.4 mmol) in THF (100 mL) and HMPA (15.5 mL, 89.2 mmol) was added *n*-butyl lithium (23.8 mL, 59.5 mmol, 2.5 M in hexanes). After warming to 0°C and stirring for 15 min, the mixture was cooled to −78°C and the hydrazone **48**[28] (13.3 mL, 59.5 mmol) was added. After 30 min, the reaction mixture was treated with a solution of the propargylic bromide **49**[29] (8.00 g, 29.7 mmol) in THF (20 mL). After 2 h, the reaction mixture was quenched with sat. aqueous NH_4Cl and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was filtered through a plug of silica gel (eluting with Et_2O) and the filtrate concentrated in preparation for the the next step. To a cold (0°C), stirred solution of the alkylated hydrazone intermediate in THF (60 mL) was added tetrabutylammonium fluoride (65.0 mL, 65.0 mmol, 1 M in THF). After warming to room temperature for 2 h, the reaction mixture was treated with sat. aqueous NH_4Cl (200 mL), the organic phase separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography afforded ketone **47** (5.00 g, 65%) as a light yellow oil; R_f=0.3 (60% EtOAc/40–60 petroleum ether); ν_{max}, cm^{-1} (film) 3433, 2921, 2843, 1719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.5 Hz), 6.86 (2H, d, J=8.5 Hz), 4.46 (2H, s), 4.25 (2H, s,), 4.06 (2H, t, J=2.1 Hz), 3.78 (3H, s), 3.07 (1H, br s), 2.64–2.58 (2H, m), 2.57–2.53 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.2, 158.8, 129.8, 129.1, 113.3, 83.2, 70.6, 67.7, 56.6, 54.7, 36.7, 29.7, 12.7; m/z (CI+) 280 ($[M+NH_4]^+$, 100%); HRMS (ES+) Found 280.1550, $[C_{15}H_{22}NO_4]^+$ requires 280.1549.

5.1.42. Oxazolone 50. To a stirred solution of ketone **47** (1.50 g, 5.70 mmol) in CH_2Cl_2 (40 mL) was added trichloroacetyl isocyanate (1.70 mL, 14.3 mmol). After 1 h, the reaction mixture was concentrated in vacuo and the residue dissolved in MeOH (60 mL). Stirring was continued and the reaction mixture was treated with K_2CO_3 (4.00 g, 28.5 mmol). After 1 h, brine (100 mL) and Et_2O (100 mL) were added, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was used directly in the next step. To a stirred solution of the crude product in toluene was added 4 Å molecular sieves (2 g). After heating at 110°C for 1.5 h, the reaction mixture was cooled, filtered and concentrated in vacuo. Flash chromatography (50% Et_2O/30–40 petroleum ether) afforded oxazolone **50** as a yellow semi-solid (800 mg, 49%); R_f=0.15 (20% EtOAc/40–60 petroleum ether); ν_{max}, cm^{-1} (film) 3156, 2935, 2854, 1746, 1613; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.85 (1H, br s), 7.25 (2H, d, J=8.6 Hz), 6.85 (2H, d, J=8.6 Hz), 6.62 (1H, s), 4.50 (2H, s), 4.10 (2H, t, J=1.8 Hz), 3.78 (3H, s), 2.57–2.53 (2H, m), 2.51–2.48 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8, 157.2, 129.1, 128.8, 125.3, 124.2, 113.3, 83.8, 77.3, 70.7, 56.6, 54.7, 22.8, 16.8; m/z (CI+) 288 ($[M+H]^+$, 20%), 305 ($[M+NH_4]^+$, 95%); HRMS (ES+) Found 305.1499, $[C_{16}H_{21}N_2O_4]^+$ requires 305.1501.

5.1.43. Oxazole 52. To a cold (−10°C), stirred solution of oxazolone **50** (40 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added sequentially 2,6-lutidine (500 μL, 4.26 mmol) and trifluoromethanesulfonic anhydride (587 μL, 3.57 mmol). After 1 h, the reaction mixture was diluted with H_2O (10 mL), the organic phase separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (20% Et_2O/30–40 petroleum ether) afforded the intermediate triflate **46** which was used directly in the next reaction. To a stirred solution of the prepared triflate in 1,4-dioxan (6 mL) was added $Pd(PPh_3)_4$. After 10 min, the reaction mixture was treated sequentially with alkyne **51**[6a] (335 μL, 0.297 mmol), copper-(I)-iodide (64.0 mg, 0.29 mmol) and 2,6-lutidine (857 μL, 7.41 mmol). After 7 h, the reaction mixture was diluted with EtOAc (4 mL) and 10% aqueous citric acid (4 mL), the organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (70% Et_2O/30–40 petroleum ether) afforded the oxazole **52** (445 mg, 49%) as a yellow oil; R_f=0.35 (60% EtOAc/40–60 petroleum ether); ν_{max}, cm^{-1} (film) 3313, 2932, 2844, 1725, 1703, 1610, 1245; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, s), 7.23 (2H, d, J=8.7 Hz), 6.85 (2H, d, J=8.7 Hz), 5.14 (1H, br s), 4.44 (2H, s), 4.19 (2H, d, J=7.5 Hz), 4.06 (2H, t, J=2.0 Hz), 3.78 (3H, s), 3.68 (3H, s), 2.72 (2H, t, J=7.1 Hz), 2.57 (2H, tt, J=7.0, 1.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.5, 157.7, 146.9, 141.6, 136.9, 130.9, 130.7, 115.0, 89.3, 86.7, 72.6, 72.2, 58.4, 56.5, 53.8, 32.4, 26.9, 19.3; m/z (CI+) 383 ($[M+H]^+$, 100%), 400 ($[M+NH_4]^+$, 20%); HRMS (ES+) Found 383.1603, $[C_{21}H_{23}N_2O_5]^+$ requires 383.1607.

5.1.44. Alcohol 53. To a stirred solution of oxazole **52** (265 mg, 0.69 mmol) in CH_2Cl_2 (7 mL) and pH 7 buffer (0.7 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (234 mg, 1.04 mmol). After 3 h, the reaction mixture was treated with sat. aqueous $NaHCO_3$ (10 mL), the organic phase separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with sat. aqueous $NaHCO_3$, dried (Na_2SO_3),

and concentrated in vacuo. Purification by flash chromatography (Et_2O) afforded the alcohol **53** (60 mg, 98%) as a colourless solid; Mp=95–98°C; R_f=0.30 (80% EtOAc/40–60 petroleum ether); ν_{max}, cm^{-1} (film) 3299, 2932, 2877, 1719; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, s), 5.28 (1H, br s), 4.22–4.18 (4H, m), 2.70 (2H, t, J=7.1 Hz), 2.57 (2H, tt, J=7.0, 1.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.0, 148.2, 142.8, 138.2, 90.7, 87.2, 81.9, 73.8, 55.1, 53.7, 33.8, 28.1, 20.5; *m/z* (*CI*+) 263 ($[M+H]^+$, 50%); HRMS (ES+) Found 263.1029, $[C_{13}H_{15}N_2O_4]^+$ requires 263.1032.

5.1.45. Acid 3. To a stirred solution of alcohol **53** (52 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added TEMPO (8 mg, 0.06 mmol) followed by iodobenzene diacetate (188 mg, 0.59 mmol). After 2 h, the reaction mixture was treated with 5% aqueous $Na_2S_2O_3$ (1 mL) and sat. aqueous $NaHCO_3$ (1 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O, the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was filtered through a small plug of silica gel (eluting with 50% Et_2O) and the filtrate concentrated in vacuo to afford the corresponding aldehyde intermediate which was used directly in the next step. To a stirred solution of the above aldehyde in *t*-BuOH (1 mL) was added methyl-2-butene (ca. 0.5 mL) in *t*-BuOH (0.5 mL), followed by cooling to 0°C and addition of a solution of $NaClO_2$ (62 mg, 0.68 mmol) and NaH_2PO_4 (309 mg, 2.04 mmol) in H_2O (1 mL). After 1.5 h, the reaction mixture was diluted with brine (4 mL) and EtOAc (4 mL), the organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Trituration with Et_2O afforded the acid **3** (90 mg, 98%) as a light yellow solid; mp=154–155°C; R_f=0.1 (EtOAc); ^1H NMR (400 MHz, CD_3OD) δ 7.74 (1H, s), 4.13 (2H, br s), 3.66 (3H, s), 2.78 (2H, t, J=7.1 Hz), 2.67 (2H, t, J=6.9 Hz); ^{13}C NMR (100.6 MHz, CD_3OD) δ 156.5, 147.9, 141.2, 138.5, 134.7, 91.2, 88.6, 75.5, 71.2, 58.3, 31.9, 25.7, 18.8; *m/z* (ES+) 277 ([M+H]+, 50%), 294 ($[M+NH_4]^+$, 55%), 299 ($[M+Na]^+$, 100%), (ES−) 275 ($[M-H]^-$, 100%); HRMS (ES+) Found 277.0823, $[C_{13}H_{13}N_2O_5]^+$ requires 277.0824.

5.1.46. Ester 54. To a cold (0°C), stirred solution of alcohol **32** (25 mg, 0.057 mmol) and acid **3** (79 mg, 0.258 mmol) in toluene (2 mL) and THF (1.3 mL) was added triphenylphosphine (300 mg, 1.14 mmol) and diethyl azodicarboxylate (33 μL, 0.19 mmol). After warming to room temperature and stirring for 14 h, the reaction mixture was concentrated in vacuo. Flash chromatography (40% Et_2O/30–40 petroleum ether) gave the ester **54** as a colourless glass (35 mg, 90%); R_f=0.4 (50% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+26.3 (*c*. 2.1, $CHCl_3$); ν_{max}, cm^{-1} (film) 2938, 2868, 1682, 1611, 1244; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (1H, t, J=0.9 Hz), 5.73 (1H, m), 5.36 (1H, ddt, J=12.2, 6.3, 1.1 Hz), 5.26 (1H, br t, J=2.9 Hz), 4.96 (1H, br s), 4.25 (2H, d, J=6.2 Hz), 4.04 (1H, dddd, J=11.4, 11.4, 4.0, 1.9 Hz), 3.89 (1H, br d, J=10.2 Hz), 3.71 (3H, s), 3.60–3.51 (3H, m), 3.34 (3H, s), 2.83 (2H, t, J=7.2 Hz), 2.71 (2H, td, J=7.0, 0.8 Hz), 2.56 (1H, dd, J=13.1, 4.0 Hz), 2.44 (1H, br dd, J=13.9, 12.2 Hz), 2.32 (1H, dd, J=13.1, 11.4 Hz), 1.92–1.86 (5H, m), 1.77 (1H, br tt, J=8.2, 1.4 Hz), 1.74–1.73 (1H, m), 1.61–1.34 (9H, m), 1.18 (3H, d, J=7.1 Hz), 1.04 (1H, ddd, J=17.1, 11.0, 2.5 Hz), 0.85 (3H, d, J=6.7 Hz), 0.84 (3H, d, J=6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 152.9, 139.5, 137.8, 132.4, 130.2, 88.3, 88.1, 73.9, 73.7, 73.6, 73.2, 71.3, 70.9, 69.9, 69.8, 69.3, 63.1, 57.2, 52.6, 43.3, 42.8, 41.6, 39.3, 39.1, 35.6, 35.6, 35.3, 31.1, 31.0, 28.1, 27.1, 24.6, 24.3, 22.2, 22.1, 18.3, 18.1; *m/z* (CI+) 697 ($[M+H]^+$, 80%); HRMS (ES+) Found 697.3689, $[C_{38}H_{53}N_2O_{10}]^+$ requires 697.3700.

5.1.47. Synthetic (+)-leucascandrolide A (1). To a stirred solution of ester **54** (25 mg, 0.036 mmol) in EtOAc (2 mL) was added palladium 5% wt. on $CaCO_3$ poisoned with lead (Lindlar cat.) (5 mg). After 10 min, the reaction mixture was treated with quinoline (4 μL, 0.04 mmol) and stirring was continued for 3 h under a baloon of H_2. The reaction mixture was filtered through Celite® (eluting with EtOAc) and concentrated in vacuo. Flash chromatography (40% Et_2O/30–40 petroleum ether) afforded (+)-leucascandrolide A (23 mg, 92%) as a colourless glass; R_f=0.4 (60% EtOAc/40–60 petroleum ether); $[\alpha]_D^{20}$=+40.0 (*c*. 0.3, EtOH), cf. Lit.[3] $[\alpha]_D^{20}$=+41.0 (*c*. 0.29, EtOH); ν_{max}, cm^{-1} (film) 3346 (N–H), 2942 (C–H), 2890 (C–H), 1725 (C=O), 1708 (C=O), 1632 (C=C); ^1H NMR (500 MHz, C_5D_5N) δ 8.34 (1H, br t, J=5.4 Hz, N*H*), 7.61 (1H, s, *H*-7′), 6.41 (1H, dt, J=11.8, 1.6 Hz, *H*-9′), 6.31 (1H, dt, J=11.5, 7.3 Hz, *H*-3′), 6.27 (1H, dt, J=12.0, 6.0 Hz, *H*-10′), 5.97 (1H, dt, J=11.5, 1.7 Hz, *H*-2′), 5.82 (1H, br dt, J=15.5, 7.2 Hz, *H*-19), 5.76 (1H, br dd, J=11.7, 6.6 Hz, *H*-17), 5.59 (1H, ddt, 15.4, 6.9, 1.3 Hz, *H*-18), 5.41 (1H, m, *H*-5), 4.78 (2H, br t, J=4.9 Hz, *H*-11′), 4.31 (1H, dddd, J=11.8, 11.5, 3.3, 2.1 Hz, *H*-3), 4.09 (1H, br d, J=12.3 Hz, *H*-11), 3.90 (1H, br t, J=12.0 Hz, *H*-9), 3.87 (1H, br dd, J=11.7, 11.3 Hz, *H*-7), 3.81 (1H, br dd, J=10.6, 10.5 Hz, *H*-15), 3.73 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.21 (2H, br q, J=7.5 Hz, *H*-4′), 2.74 (2H, br t, J=7.4 Hz, *H*-5′), 2.71 (1H, dd, J=13.0, 3.7 Hz, *H*-2), 2.49 (1H, br dd, J=14.1, 12.0 Hz, *H*-10), 2.45 (1H, dd, J=13.1, 11.6 Hz, *H*-2), 2.06 (1H, ddd, J=11.8, 11.3, 2.3 Hz, *H*-8), 1.96 (1H, br d, J=13.7 Hz, *H*-4), 1.90-1.88 (1H, m, *H*-16), 1.89 (1H, br d, J=13.9 Hz, *H*-6), 1.88 (2H, br dd, J=7.0, 6.9 Hz, *H*-20), 1.84–1.86 (1H, m, *H*-13), 1.78 (1H, ddd, J=14.0, 10.5, 2.2 Hz, *H*-16), 1.62 (1H, ddd, J=14.2, 11.5, 2.7 Hz, *H*-6), 1.55–1.53 (1H, m, *H*-21), 1.51 (1H, ddd, J=14.0, 3.1 Hz, *H*-4), 1.50–1.47 (1H, m, *H*-14), 1.43–1.41 (1H, m, *H*-12), 1.33–1.31 (1H, m, *H*-8), 1.30 (1H, br d, J=13.8 Hz, *H*-13), 1.25 (1H, br d, J=14.1 Hz, *H*-14), 1.12 (3H, d, J=7.0 Hz, *H*-24), 1.08 (1H, ddd, J=14.4, 11.6, 2.7 Hz, *H*-10), 0.83 (3H, d, J=6.6 Hz, *H*-22), 0.82 (3H, d, J=6.6 Hz, *H*-23); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 165.3, 160.1, 157.1, 149.2, 141.1, 136.4, 133.9, 132.4, 130.1, 120.7, 116.6, 73.6, 73.3, 70.8, 70.0, 69.6, 67.3, 63.1, 57.3, 52.2, 43.3, 42.8, 41.6, 39.4, 39.3, 35.6, 35.5, 35.5, 31.0, 28.1, 27.7, 27.2, 25.7, 24.3, 22.2, 18.3; *m/z* (ES+) 701 ($[M+H]^+$, 70%), 723 ($[M+Na]^+$, 100%); HRMS (ES+) Found 701.4014, $[C_{38}H_{57}N_2O_{10}]^+$ requires 701.4013. This spectroscopic data was in agreement with that reported by Pietra and co-workers for natural (+)-leucascandrolide A.[3,31]

Acknowledgements

We thank the EPSRC (studentship to M. T. and

GR/N08520), the EC (Network HPRN-CT-2000-00018), and Merck, Pfizer, and Novartis Pharma AG for support.

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