Pergamon

Tetrahedron, Vol. 52, No. 5, pp. 1811-1834, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01015-7

Total Synthesis of (–)-Denticulatins A and B Using Efficient Methods of Acyclic Stereocontrol.

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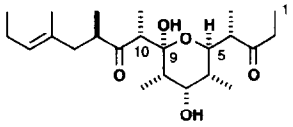
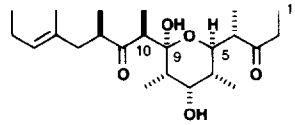
Abstract: The total synthesis of (–)-denticulatin B (**2**) was achieved in 9 steps (20% yield), with 70% overall diastereoselectivity, starting from the ethyl ketone (*R*)-**9**. Most of the stereochemistry was introduced by substrate-based control. Key steps include the boron-mediated aldol/reduction, **9** → **22**, the titanium-mediated aldol coupling, **26** + **8** → **38**, and the directed cyclisation, **35** → **2**. Epimerisation at C_{10} in **35** led to (–)-denticulatin A (**1**).

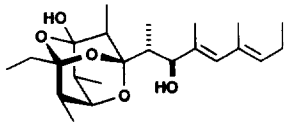
Pulmonates of the genus *Siphonaria*, commonly known as false limpets, are air-breathing molluscs, which live in the intertidal zone on rock platforms, feeding on encrusting algae and microorganisms. These marine molluscs are a rich source of polypropionate-derived natural products.[1,2] Denticulatin A (**1**) and denticulatin B (**2**) were first isolated in 1983 by Faulkner's group from *Siphonaria denticulata*,[1] collected from the coast of New South Wales, Australia. Related polypropionate metabolites from pulmonate molluscs include muamvatin (**3**)[2a,3] and siphonarin B (**4**).[2b,4]



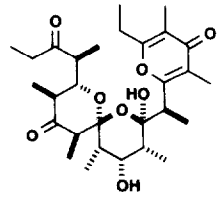
denticulatin A (1)



denticulatin B (2)



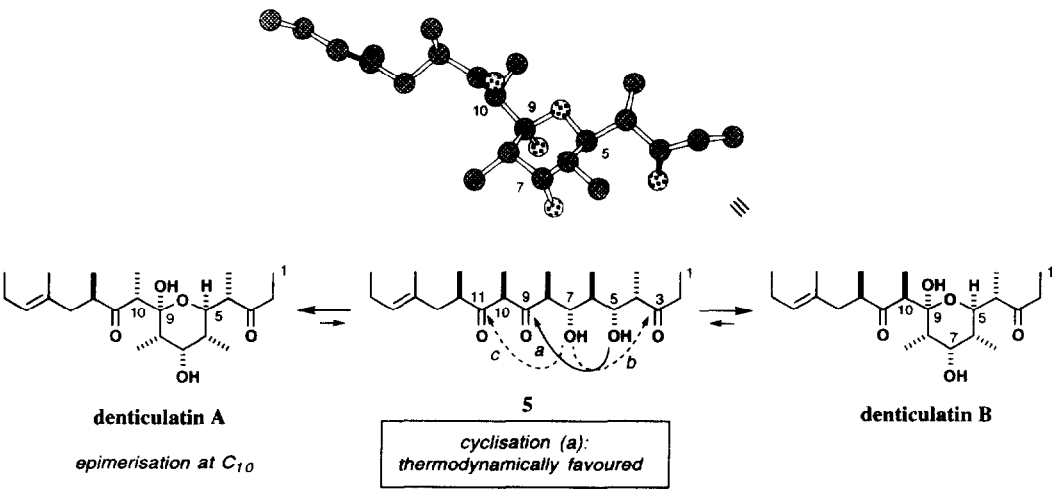
muamvatin (3)



siphonarin B (4)

The siphonariid metabolites **1**–**4** are characterised structurally as being highly substituted, tetrahydropyranyl acetals or hemiacetals containing 8 to 10 stereocentres. Their high level of oxygenation, with methylation at alternate carbons, is indicative of their polypropionate origin. Indeed, biosynthetic studies have confirmed that the denticulatins[5] and siphonarins[4a] are produced by the linear combination of propionate units. While these marine natural products are related structurally and biosynthetically to the macrolide and polyether antibiotics of bacterial origin, they show negligible antimicrobial activity and their biological function is uncertain.

The structure of denticulatin B (**2**) was determined by spectroscopic methods and X-ray crystallography.[1] Other than an epimeric relationship at C_{10}, denticulatin A (**1**) and B (**2**) are identical. Indeed, base treatment of denticulatin B is reported to give an equimolar mixture of denticulatin A and B. As shown in **Scheme 1**, C_{10} epimerisation is facilitated by equilibration with the corresponding open-chain form, β-diketone **5**. Note that there are three possible, hemiacetal-forming, cyclisation modes for **5**: (*a*) the C_5 hydroxyl adding to the C_9 ketone; (*b*) the C_7 hydroxyl adding to the C_3 ketone; (*c*) the C_7 hydroxyl adding to the C_{11} ketone. Cyclisation mode (*a*) is preferred thermodynamically, wherein all four alkyl ring substituents become equatorial and the hemiacetal oxygen at C_9 is in the anomerically-favoured axial position, while the axial orientation of the C_7 hydroxyl enables hydrogen bonding to the anomeric oxygen. A configurational model for siphonariid metabolites has recently been proposed, which rationalises the stereochemistry of the acyclic precursors of denticulatin A (**1**), muamvatin (**3**) and siphonarin B (**4**), where the observed acetal ring systems are determined by thermodynamic factors related to the oxidation state of the carbons and the configurations of the hydroxyl and methyl groups in the respective acyclic precursors.[6]



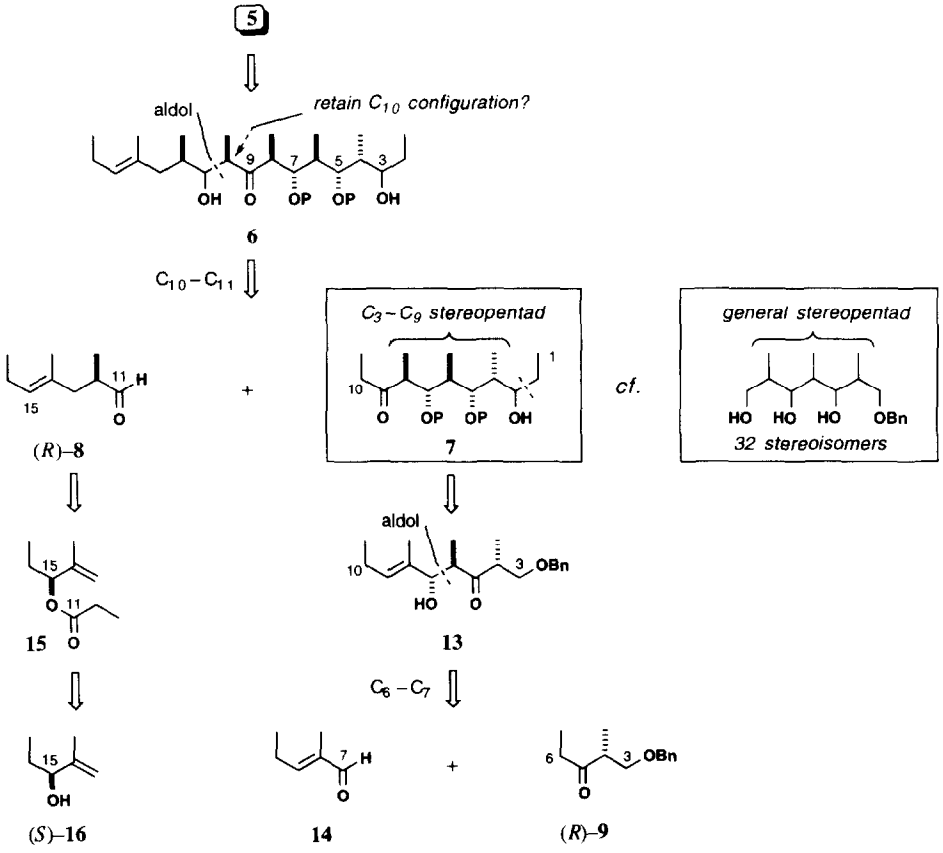
Scheme 1

The first total synthesis, reported by Ziegler and Becker in 1990,[7] generated denticulatin A and B as a mixture from a protected version of the open-chain precursor (*cf.* **5**). The acidic deprotection conditions employed led to decomposition, such that only a low conversion could be realised. A more recent synthesis, reported by Hoffmann *et al.*,[8] cleverly uses the isomerisation of one of the alternative ring systems to secure the denticulatin hemiacetal. While Hoffmann's denticulatin precursor was configurationally homogeneous at C_{10}, the deprotection protocol resulted in epimerisation at C_{10}. In both these earlier syntheses,[9] Ziegler and Hoffman used their own strategies for controlling stereochemistry in the assembly of the polypropionate skeleton of the denticulatins. Similarly, we viewed the denticulatins (as well as the related siphonariid metabolites, muamvatin[3a] and siphonarin B[4b]) as an excellent test for our general aldol-based strategy for the construction of polypropionate-derived natural products.[10]

Our objectives in this project were two-fold: (*i*) to use substrate-based control to quickly build up an acyclic precursor of the denticulatins with the required stereochemistry; (*ii*) to achieve efficient cyclisation, avoiding epimerisation at C_{10}, to selectively form denticulatin A or B. In this paper, we report full details[11] of a short and efficient synthesis of the denticulatins, which realises both of these objectives.

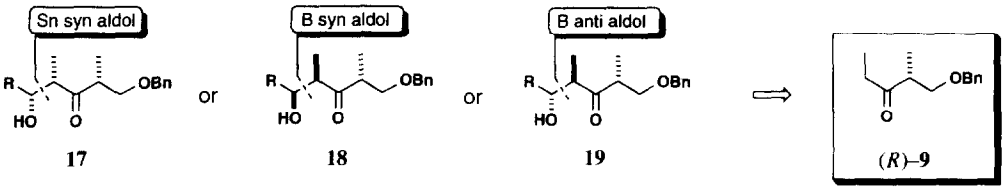
Synthetic Strategy Adopted for Denticulatin A and B

Denticulatin A (**1**) and B (**2**) appeared to be ideal targets for illustration of our general stereopentad approach to polypropionate synthesis.[10-12] Our synthesis plan, as outlined in **Scheme 2**, is based on aldol-type disconnections of the C_{10}–C_{11} and C_6–C_7 bonds. Alternative aldol approaches were also considered, but not pursued as they would necessitate a longer synthesis or provide less reliable stereocontrol. As already discussed, the required hemiacetal ring system of the denticulatins should be accessible by cyclisation of the respective acyclic precursor, *i.e.* **5** → **2** or 10-*epi*-**5** → **1**. Following this plan, a stereoselective synthesis of denticulatin B relies on control at C_{10} in the β-hydroxyketone **6** by a suitable aldol coupling between ethyl ketone **7** and aldehyde **8**. The resulting C_{10} stereocentre in **6** would then need to be preserved over the remaining steps of the synthesis, including oxidation at C_3 and C_{11}, deprotection of the C_5 and C_7 hydroxyls and final cyclisation. This would require a careful choice of the hydroxyl protecting group used in the synthesis.



Scheme 2

The six contiguous stereocentres spanning C_1–C_{10} in the ethyl ketone **7** were a key consideration in our synthetic strategy. We have previously developed a general protocol for the synthesis of stereopentads from the appropriate enantiomer of ethyl ketone **9**, whereby selective access to all 32 possible stereoisomers was demonstrated.[12a] This chiral ketone functions as a versatile and powerful dipropionate reagent for the synthesis of polypropionate-derived natural products and has been widely used in our laboratory. By appropriate choice of the enolate derivative of ketone **9**, as summarised in **Scheme 3**, three out of the four possible aldol diastereomers are readily accessible. The syn-syn isomer **17** is available using the tin(II) enolate,[13a] the syn-anti isomer **18** using the appropriate *Z*-enol diisopinocampheylborinate,[13b] while the anti-anti isomer **19** is obtained efficiently using the *E*-enol dicyclohexylborinate.[13c] In this particular case, the appropriate precursor of **7** is the anti-anti aldol adduct **13** derived from (*R*)-**9** and enal **14** (the simple aldol dimer of acetaldehyde).[13c] The elaboration of **13** into **7** in **Scheme 2** would then be patterned after our general protocol for stereopentad synthesis,[12] requiring stereocontrolled ketone reduction at C_5 and alkene hydroboration, as well as introduction of the terminal ethyl group at C_3 with its associated (temporary) stereocentre. The chiral aldehyde (*R*)-**8**, required for coupling with **7**, should be available from an Ireland-Claisen rearrangement[14] performed on **15**, which would be derived in turn from the allylic alcohol (*S*)-**16**.[15]



Scheme 3

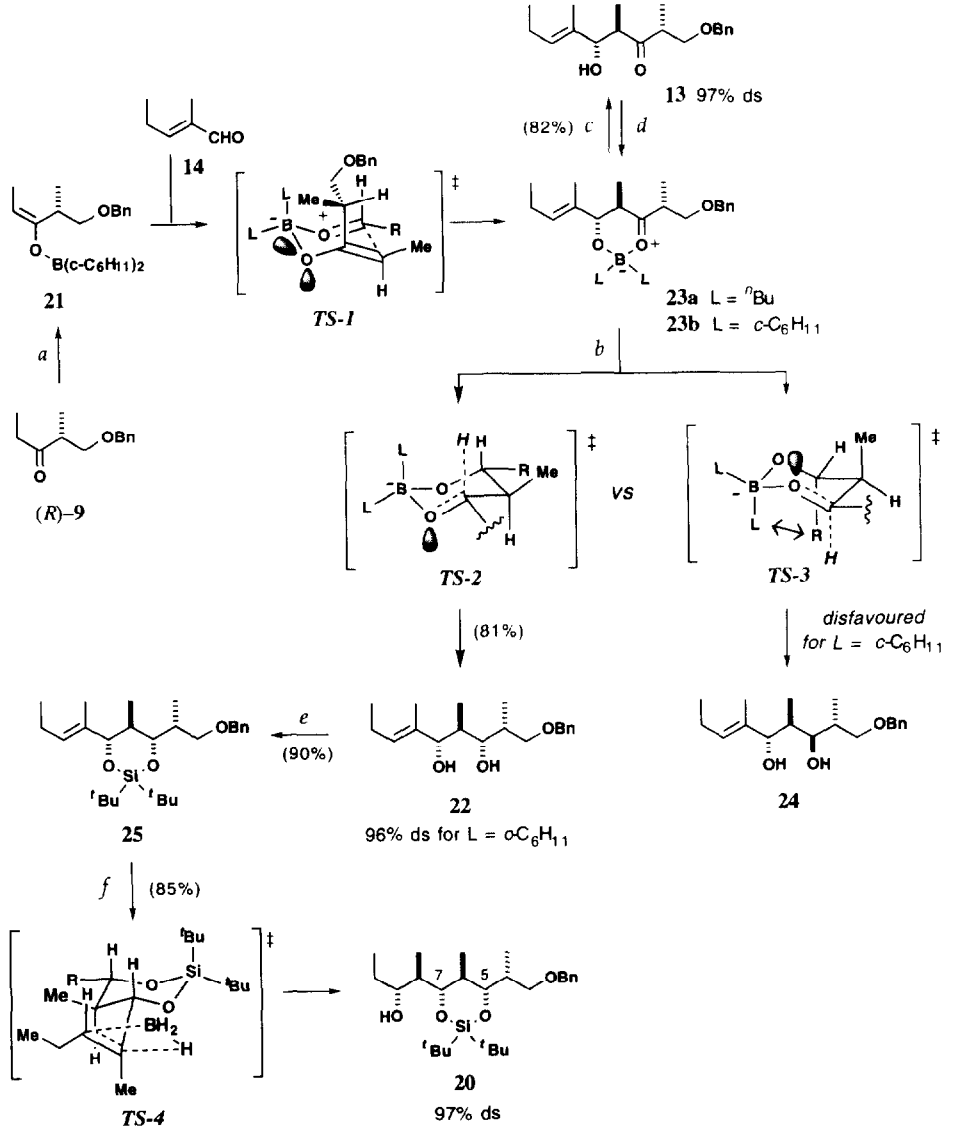
Synthesis of the C_1–C_{10} ketone 26.

The synthesis of the C_3–C_{10} subunit **20**, with the two hydroxyl groups at C_5 and C_7 protected as the cyclic di-*tert*-butylsilylene derivative, is shown in **Scheme 4**. The choice of this protecting group was critical as it had been found previously by Zeigler and Becker[7] that the denticulatins were susceptible to decomposition even under mild acidic conditions. We anticipated that this silyl protecting group would be removed under mild conditions using buffered HF-pyridine[16] as the final, hemiacetal-forming, step of our synthesis.

The synthesis of **20** starts out with a stereocontrolled aldol coupling between the chiral ketone **9**[12,13] and the six-carbon enal **14** to provide the C_1–C_5 segment. Addition of the *E*-enol dicyclohexylborinate **21**, obtained by enolisation of (*R*)-**9** with $(c\text{-}C_6H_{11})_2BCl/Et_3N$, to (*E*)-2-methyl-2-pentenal (**14**) gave on oxidative work-up the expected[12e,13c] anti-anti aldol isomer **13** in 82% yield. Careful analysis of the crude product mixture by HPLC and ^1H NMR indicated that the reaction diastereoselectivity was at least 97% ds, in good agreement with other examples from our laboratory. We believe that the high level of π-face selectivity shown by this particular enol borinate results from the aldol reaction proceeding through the preferred chair transition structure, ***TS-I***, where steric A(1,3) strain is minimised and lone-pair repulsion between the benzyl ether and the enolate oxygens is avoided.[17]

Reduction to the corresponding syn 1,3-diol **22** was first attempted using a modified Narasaka reduction,[18] involving initial formation of the boron chelate from the β-hydroxyketone. Treatment of the di-*n*-butylboron chelate **23a** derived from **13** ($^nBu_2BOMe$, THF, MeOH) with $LiBH_4$ led to an *ca* 60:40 inseparable

mixture of diols **22** and **24**, indicating poor reduction stereoselectivity. This result was not too surprising as Narasaka had reported that anti aldols gave inferior levels of stereocontrol relative to other substrates.[18] It was also possible that the boron chelate was not being formed completely and competitive reduction of the uncomplexed β-hydroxyketone **13** was taking place. Other reduction methods investigated also proved unsatisfactory. Fortunately, this problem was easily overcome by employing a novel one-pot sequence, where the boron aldolate resulting from the initial aldol addition was reduced *in situ*.



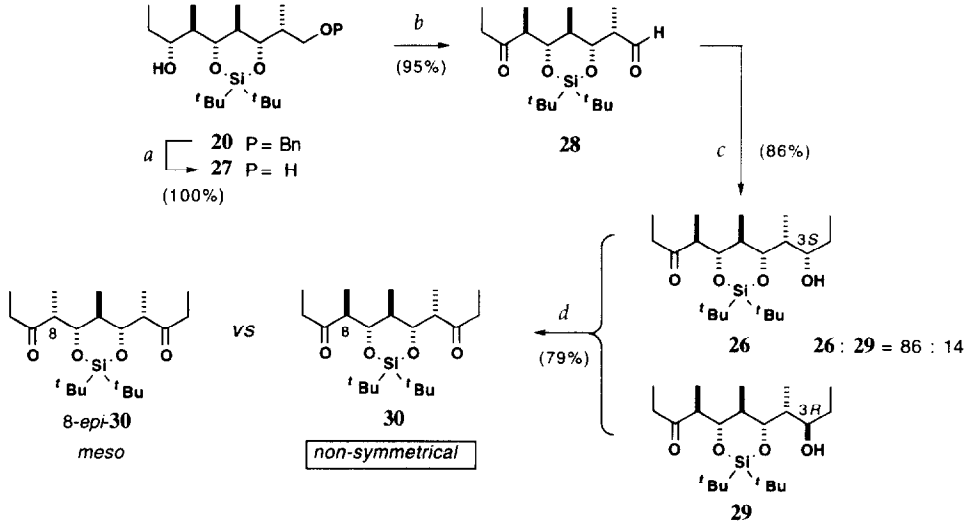
Scheme 4: (*a*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, –15 °C, 2 h; **14**, 2 h; (*b*) $LiBH_4$, 1 h, –78 °C; H_2O_2, 10% NaOH, MeOH, 2 h; (*c*) H_2O_2, MeOH-pH7 buffer; (*d*) $^nBu_2BOMe$, THF-MeOH, –78 °C; (*e*) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 4 h; (*f*) $BH_3{\bullet}SMe_2$, THF, 20 °C, 18 h; H_2O_2, 10% NaOH, THF, 21 h.

When the intermediate dicyclohexylboron aldolate **23b**, formed as before from (*R*)-**9** and **14**, was reduced with $LiBH_4$, this provided the required syn 1,3-diol **22** with dramatically improved diastereoselectivity (96% ds). Since the aldol stereocontrol had already been determined as ≥97% ds, this indicated that the reduction stereocontrol was near perfect. The reduction gave an unusually stable cyclic boronate, which was best purified by silica gel chromatography then oxidised using basic hydrogen peroxide to give **22** in 81% yield. The syn 1,3-diol relationship was determined by ^{13}C NMR analysis of the acetonide derivative,[19] which showed diagnostic resonances at δ 97.8, 30.1 and 19.8 ppm. Assuming both reductions occur through the chelated structures **23a–b**, this ligand effect may be rationalised as follows. With *n*-butyl ligands on boron in **23a**, reduction can take place through the competing chair-like transition structures ***TS-2*** (R and Me equatorial with gauche interaction) giving **22** and ***TS-3*** (R and Me now axial with L ↔ R diaxial interaction) giving **24**. For the more sterically demanding cyclohexyl ligands, however, the L ↔ R interaction in ***TS-3*** becomes more severe and high reduction stereoselectivity ensues by preferred axial attack of hydride *via* ***TS-2***. Note that this aldol-reduction protocol using the dipropionate reagent **9** serves to introduce three new stereocentres in a highly reliable fashion. This one-pot procedure has been exploited in several other situations for the expedient preparation of stereotetrads related to **22**.[12a,20]

Having satisfactorily set up the stereotetrad spanning C_4–C_7, introduction of the cyclic silicon protecting group at the C_5 and C_7 hydroxyl groups was now required. Treatment of **22** with $^tBu_2Si(OTf)_2$/lutidine in CH_2Cl_2 led to the silylene[21] derivative **25** in 90% yield. We now needed to achieve a stereocontrolled hydration of the trisubstituted alkene in **25**. Hydroboration of **25** using $BH_3{\bullet}SMe_2$ in THF, followed by an extended oxidative workup, gave **20** with 97% ds in 85% yield. The boronate ester produced by peroxide treatment proved relatively resistant to hydrolysis and required prolonged exposure to base. The remarkably high level of 1,2-anti selectivity achieved in this hydroboration of an allylic silyl ether using a sterically undemanding borane is notable. Normally, such hydroborations require the use of a bulky borane like thexylborane or 9-BBN.[22] The conformational rigidity and steric demands of the di-*tert*-butylsilylene group clearly contribute to this result. We propose that the preferred transition structure for the addition of borane to the alkene in **25** is represented by ***TS-4***, where the rear π-face is sterically shielded from attack by the methyl substituent at C_6. Thus the C_3–C_{10} segment **20** is obtained in 61% yield in effectively only three steps from (*R*)-**9** with 93% ds for setting up the six contiguous stereocentres. The sequence can be carried out on a multi-gram scale and represents a paradigm of efficient stereocontrol in acyclic systems.

The conversion of compound **20** to the ethyl ketone **26** (*cf.* **7** in **Scheme 2**), as required for aldol coupling to aldehyde **8**, is shown in **Scheme 5**. Debenzylation of **20** by catalytic hydrogenolysis led to the crystalline diol **27** in essentially quantitative yield. Using PCC,[23] we were able to oxidise both hydroxyl groups in **27** to give the ketoaldehyde **28** (95%). This aldehyde proved unstable to chromatography and was best used immediately in the subsequent step. Completion of the synthesis of the ethyl ketone **26** now required chemoselective addition of an ethyl organometallic reagent to the aldehydic carbonyl group in **28**. Considerable experimentation was required before a satisfactory set of conditions was found. The optimum conditions involved adding EtMgBr to **28** in dilute Et_2O solution (0.1 mmol/ml) at –100 °C, warming briefly to –50 °C, and quenching with MeOH. In contrast, performing this reaction in THF gave a complex mixture of products. Both ethyl lithium and higher-order cuprates ($Et_2CNCuLi_2$) gave mixtures containing double addition products, where the ketone carbonyl group had also reacted.

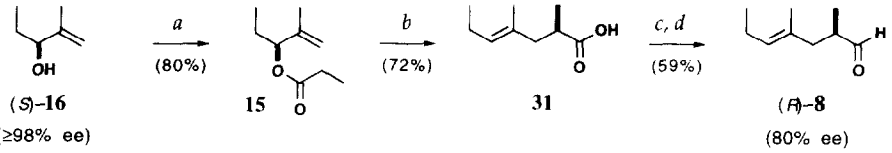
The Grignard addition provided a 86:14 mixture of isomers at the temporary C_3 stereocentre in 86% yield. The major isomer **26** was assumed to be 3*S* corresponding to the expected Felkin-Anh adduct (this was also the only mono-addition isomer isolated from the ethyl lithium reaction). At this stage, oxidation of these epimeric alcohols with PCC gave the same non-symmetrical diketone **30**. This helped to confirm that the earlier hydroboration step, **25** → **20**, had proceeded with the expected[22] 1,2-anti selectivity, since the alternative 1,2-syn[24] hydroboration product would have resulted in production of the *meso* diketone 8-*epi*-**30**. The epimeric adducts **26** and **29** were separated chromatographically and individually taken through the remaining steps of the synthesis.



Scheme 5: (*a*) H_2, 10% Pd/C, EtOH, 20 °C, 6 h; (*b*) PCC, CH_2Cl_2, 20 °C, 3 h; (*c*) EtMgBr, Et_2O, –100 °C, 15 min → –50 °C, 15 min; MeOH; (*d*) PCC, CH_2Cl_2, 20 °C, 18 h.

Synthesis of the C_{11}–C_{17} aldehyde (*R*)-8.

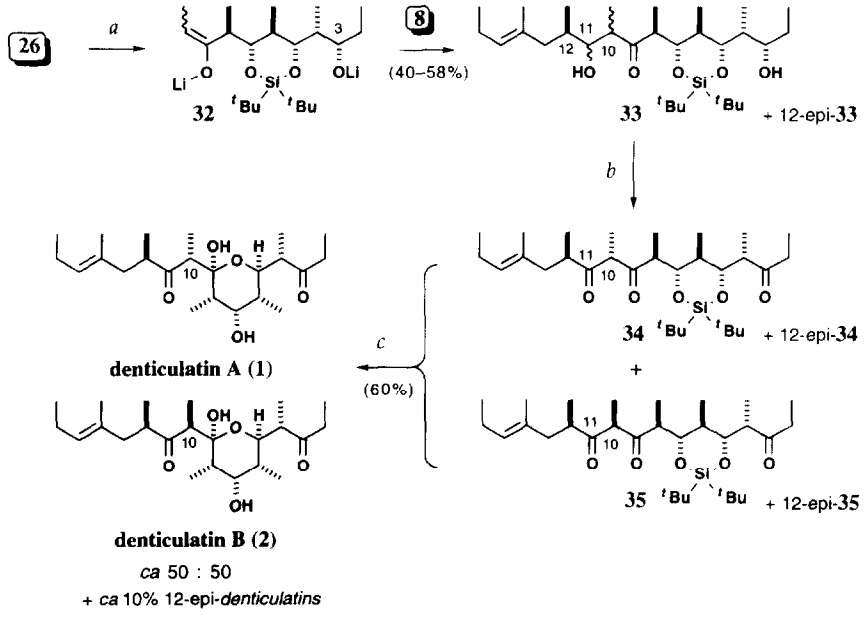
In contrast to the substrate-based synthesis of ketone **26**, our synthesis of the required aldehyde component (*R*)-**8** in **Scheme 6** now exploited reagent control. A Sharpless asymmetric epoxidation of the allylic alcohol *rac*-**16** using (–)-*D*-diisopropyl tartrate provided the kinetically-resolved (*S*)-**16**[15] in high enantiomeric purity (≥98% ee). This alcohol was converted to its propionate ester **15** using propionyl chloride in the presence of pyridine. An Ireland-Claisen rearrangement on **15**, employing standard conditions for generating the *Z* silyl ketene acetal (LDA, Me_3SiCl, THF),[25] was then used to obtain the acid **31**. Conversion into the desired aldehyde (*R*)-**8** was best achieved by reduction of the crude acid **31** to the corresponding alcohol using $LiAlH_4$ followed by oxidation with PCC. The resulting aldehyde (*R*)-**8** was somewhat unstable and was best used as soon as it was produced. ^1H NMR analysis of the (*R*)-MTPA ester[26] formed from its alcohol precursor indicated an enantiomeric purity of 80% ee. This corresponded to *ca* 90% chirality transfer in the Ireland-Claisen rearrangement step. While this level of enantiomeric enrichment was a little disappointing at the time, it was considered adequate to continue the synthesis and alternative routes to (*R*)-**8** were not pursued. Indeed, a similar route to the ethyl ketone corresponding to (*R*)-**8** was used in the earlier Hoffmann denticulatin synthesis.[8a,b]



Scheme 6: (*a*) EtCOCl, pyridine, CH_2Cl_2, 20 °C, 2 h; (*b*) Me_3SiCl, Et_3N, THF, LDA, −78 °C, 1 h → 70 °C, 4 h; 1 *M* HCl; (*c*) $LiAlH_4$, Et_2O, 0 °C, 0.5 h; (*d*) PCC, CH_2Cl_2, 20 °C, 3 h.

Aldol Coupling of ketone 26 with aldehyde (*R*)-8

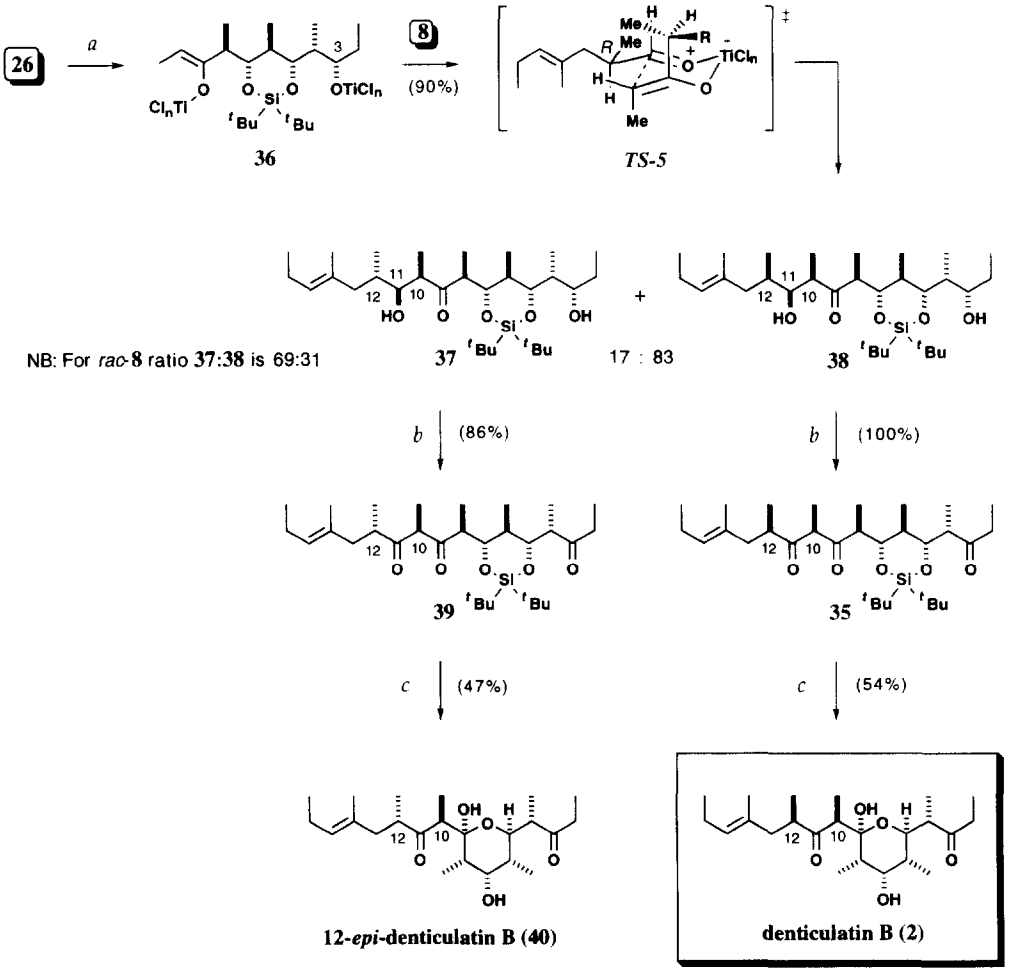
The next phase of our denticulatin synthesis required the development of a suitable set of conditions for stereocontrolled aldol coupling between the ethyl ketone **26** and aldehyde (*R*)-**8**. Since both the enolate and aldehyde components are chiral, they will each have an intrinsic π-facial bias and contribute to the observed reaction diastereoselectivity (double stereodifferentiation). To ensure a good level of stereocontrol at the C_{10} stereocentre, a suitable choice of metal enolate and control of the enolate geometry would be essential. However, this issue was temporarily postponed while we first focused on completing a preliminary synthesis of the denticulatins, as shown in **Scheme 7**.



Scheme 7: (*a*) LDA, 2.5 equiv, THF, −78 °C, 30 min; **8**, 30 min; (*b*) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 45 min, Et_3N, → 20 °C, 45 min; (*c*) HF-pyridine, pyridine, THF, 20 °C, 4 h.

We initially examined the aldol coupling between the two segments (*R*)-**8** (80% ee) and **26** (100% ee) using the lithium enolate **32**, prepared by kinetic deprotonation using LDA in THF. As expected, this gave a complex mixture of all four aldol isomers **33** in moderate yield (40–58%), which could not be separated easily and also contained adducts derived from the minor (*S*)-enantiomer of the aldehyde component. This mixture of aldol adducts was oxidised under standard Swern conditions[27] to give the triketones **34** and **35** as a roughly

equimolar mixture (containing small amounts of their respective epimers at C_{12}). Notably ^1H NMR analysis showed no evidence for the presence of enol tautomers of the β-dicarbonyl system. Following deprotection of this mixture by HF/pyridine, inspection of the ^1H NMR spectrum indicated that a roughly 50:50 mixture of denticulatin A (**1**) and B (**2**) had been produced by cyclisation of the C_5 hydroxyl onto the C_9 ketone (together with minor contaminating isomers at C_{12} arising from aldol addition to (*S*)-**8**). This served to demonstrate that the di-*tert*-butylsilylene protecting group could be removed efficiently without noticeable dehydration, which had previously been observed to be a serious competing process for other diol protecting groups.[7,8] Note also that this coupling-oxidation sequence avoided the need for hydroxyl protection at C_3. However, this route suffered from poor selectivity in the aldol coupling step, which also gave variable yields.



Scheme 8: (*a*) $TiCl_4$, 3 equiv, CH_2Cl_2, –78 °C, 30 min; $^iPr_2NEt$, 3.5 equiv, 1 h; **8**, 15 min; (*b*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 45 min, Et_3N, → 0 °C, 5 min; (*c*) HF-pyridine, pyridine, THF, 20 °C, 4 h.

A suitable stereoselective aldol coupling between **26** and (*R*)-**8** would allow the first selective synthesis of denticulatin A or B, provided subsequent epimerisation at C_{10} could be avoided. After some unpromising

initial experiments with boron and tin(II) enolates, this was achieved as shown in **Scheme 8** by using the highly reactive titanium(IV) enolate. The *Z* titanium enolate **36** could be easily generated from the ethyl ketone **26** under modified Evans conditions[28] ($TiCl_4$, 3 equiv, 30 min, –78 °C; $^iPr_2NEt$, 3.5 equiv, 1 h). Addition of the aldehyde (*R*)-**8** (80% ee, 3 equiv) then gave a separable 17:83 mixture of the two 8,10-syn-10,11-syn aldol adducts **37** and **38**. The major isomer **38** corresponding to aldol addition to (*R*)-**8** was now obtained in 75% yield. This was taken on to give denticulatin B. The minor isomer **37** was derived from the small amount of enantiomeric aldehyde present – this was taken on to give 12-*epi*-denticulatin B.

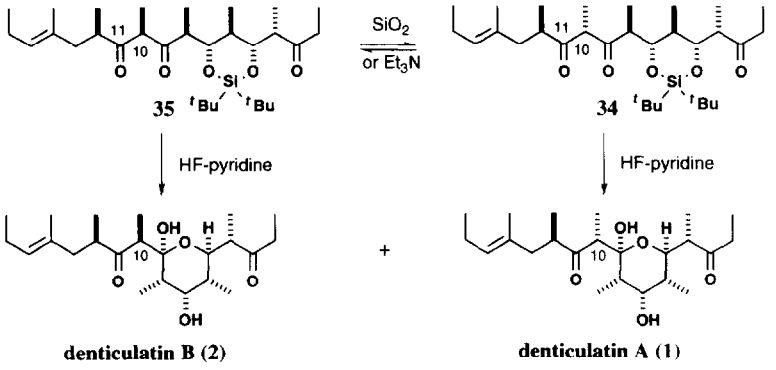
Thus enolate **36** shows a high level of diastereoface selectivity, which agrees with previous results for such titanium aldol reactions described by the Evans group,[28-30] as well as related boron enolate reactions.[31] A common transition state model has been proposed for asymmetric induction in such situations, which would suggest that ***TS-5*** is the preferred pathway for reaction with (*R*)-**8** leading to **38**. There is some kinetic discrimination occurring in this reaction with the enantiomeric aldehyde reacting faster, resulting in a lower ratio of diastereomers than that anticipated from the 90:10 enantiomeric ratio for **8**. The π-face selectivity arising from the chiral enolate component is matched[32] with the anti-Felkin preference[33] of the minor (*S*)-enantiomer of the aldehyde. In other words, the desired coupling with (*R*)-**8** is mismatched.[32] In support of this hypothesis, use of the racemic aldehyde *rac*-**8** led to a 69:31 ratio of isomers **37** and **38** in 90% yield. Similarly, the minor C_3 epimer **29** (see **Scheme 5**) was taken through the titanium-mediated aldol coupling with aldehyde (*R*)-**8** (80% ee) to give adducts 3-*epi*-**37** and 3-*epi*-**38** in a ratio of 25:75.

At this stage, we found that it was necessary to carry out the Swern oxidation under carefully defined conditions minimising contact with the triethylamine base. Specifically, this involved treatment of **38** with DMSO/oxalyl chloride at –78 °C, followed by Et_3N at –78 °C, then warming to –5 °C for 5 min, and finally quenching with NH_4Cl solution to give crude triketone **35**. These precautions were taken as triethylamine completely equilibrated **35** to a 1:1 mixture with its C_{10} epimer **34** within 45 min at room temperature. Varying levels of C_{10} epimerisation also occurred on silica gel chromatography. By avoiding chromatography, the triketone **35** could be handled without significant epimerisation (<10% by ^1H NMR) at the C_{10} stereocentre. Careful Swern oxidation of 3-*epi*-**38** gave the same triketone **35**.

While apparently having solved all the synthetic problems, we were concerned that the C_{10} stereocentre might still be epimerised in the final silylene deprotection step, leading to a mixture of denticulatin A and B. Fortunately, this did not happen. Treatment of **35** with HF–pyridine, buffered by excess pyridine,[16] followed by crystallisation of the crude product mixture from pentane, gave pure (–)-denticulatin B (m.p. 135-137 °C, $[\alpha]_D^{20} = -29.3°$ (*c* 0.4, $CHCl_3$)) in 54% overall yield from **38**. Thus, we had achieved the first stereocontrolled synthesis of (–)-denticulatin B. As shown in **Scheme 9**, deliberate equilibration of the β-diketone **35** with **34** by silica gel chromatography (or Et_3N), followed by cyclisation under the same conditions as before, gave a 78% yield of an *ca* 1:2 mixture of (–)-denticulatins A ($[\alpha]_D^{20} = -35.1°$ (*c* 0.4, $CHCl_3$)) and B. The ^1H and ^{13}C NMR spectra, m.p. and $[\alpha]_D^{20}$ for each isomer were in full accord with the reported data[1] and copies of the ^1H NMR spectra for the denticulatins (provided by Dr M. J. Garson).

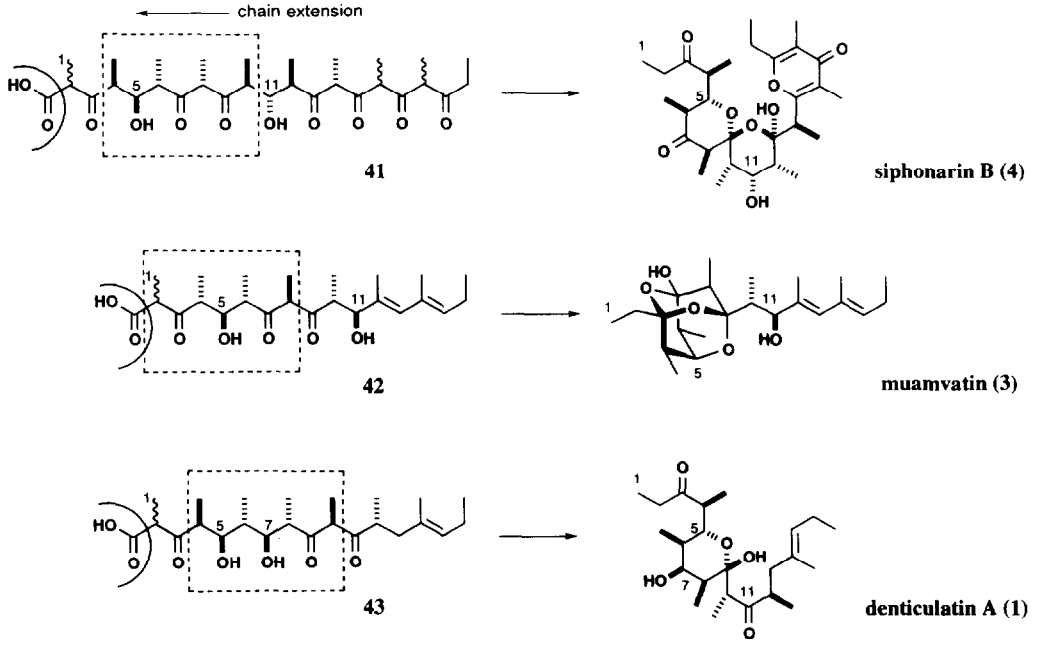
Under similar conditions, we also oxidised **37** isolated from the aldol reaction of **26** with the racemic aldehyde **8** in **Scheme 8**. Rapid chromatography led to isolation of the triketone **39** as apparently a single isomer by ^1H NMR, indicating that little or no epimerisation at C_{10} had occurred. Similarly, 3-*epi*-**37** was oxidised to give this same triketone. This compound appeared to be somewhat less susceptible to epimerisation than the corresponding triketone **35**. The triketone **39** was then deprotected by HF/pyridine to give

predominantly 12-*epi*-denticulatin B (**40**), with only minor amounts (<10%) of 12-*epi*-denticulatin A being formed. Note that a useful diagnostic signal in the ^1H NMR spectra in $CDCl_3$ for the denticulatins is the hemiacetal OH at C_9 (denticulatin B, δ 5.38; denticulatin A, δ 6.1; 12-*epi*-denticulatin B, δ 5.42; 12-*epi*-denticulatin A, δ 6.45).



Scheme 9

Pure samples of the synthetic denticulatins A and B were found to interconvert reasonably readily on silica gel. This suggests that the polypropionate metabolite isolated from *Siphonaria denticulata* may actually be only a single compound, which isomerises at C_{10} on chromatographic isolation. Based on the configurational model which we have recently proposed for siphonariid metabolites,[6] which is reproduced in **Scheme 10**, this is likely to be denticulatin A.



Scheme 10

Natural products or isolation artifacts?

Subsequent to the completion of this work, studies towards the synthesis of muamvatin (**3**) led us to speculate that some of these cyclic acetals obtained from siphonariid molluscs may be isolation artifacts.[3a] The true polypropionate metabolite may be an acyclic derivative, which is induced to cyclise on isolation. As with the denticulatins, this results in the formation of the thermodynamically-preferred acetal ring system. Thus, some of the compounds isolated from siphonariid molluscs may represent thermodynamic, *i.e.* non-enzymatic, cyclisation products of unstable acyclic polypropionate metabolites, *e.g.* **41**, **42** and **43** in **Scheme 10**. If this is also true for the denticulatins, then the authentic polypropionate from *Siphonaria denticulata* might exist as an acyclic chain with the two hydroxyls at C_5 and C_7 in **43** derivatised in some manner.

Conclusions

In summary, we have achieved a short and highly efficient synthesis of the denticulatins (9 steps in 26% yield from (*R*)-**8**). Moreover, by exploiting efficient methods of substrate-based control of acyclic stereochemistry, (–)-denticulatin B (**2**) can be obtained stereoselectively for the first time (>70% overall ds and 20% yield). It has been established that the open-chain triketone **35** is configurationally stable at C_{10} under neutral conditions but readily epimerises to give **34** by chromatography on silica gel, which then gives (–)-denticulatin A (**1**) on deprotection.

Experimental Section[34]

(*R*)-1-(Benzyloxy)-2-methylpentan-3-one (9). This was prepared according to our previously reported procedure from (*R*)-methyl 3-hydroxy-2-methylpropionate.[12c,e]

(2*R*,4*R*,5*S*,6*E*)-5-Hydroxy-2,4,6-trimethyl-1-phenylmethoxy-6-nonene-3-one (13). To a stirred solution of dicyclohexylboron chloride (0.156 ml, 0.72 mmol) in dry Et_2O (2 ml) was added Et_3N (0.106 ml, 0.77 mmol) and the mixture was cooled to –15 °C. The ketone (*R*)-**9** (0.10 g, 0.48 mmol) in Et_2O (0.5 ml) was then added *via* cannula and the reaction mixture stirred for 2 h at –15 °C. A solution of (*E*)-2-methyl-2-pentenal (**14**) (0.14 ml, 1.0 mmol) in Et_2O (5 ml) was added *via* cannula and stirring was continued at this temperature for 2 h. The reaction mixture was then partitioned between Et_2O (3 x 15 ml) and pH7 buffer solution (5 ml), the organic extracts were combined and concentrated *in vacuo* to give an oil. This residue was suspended in MeOH (3 ml), pH 7 buffer (3 ml) was added and the mixture cooled to 0 °C. Hydrogen peroxide (1.6 ml; 30% aqueous) was added dropwise and stirring continued at room temperature for 2 h. The reaction mixture was then poured into distilled water (30 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (30 ml), brine (30 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (10% Et_2O/CH_2Cl_2) gave the anti-anti aldol product **13** (0.12 g, 82%) as an oil: R_f 0.58 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –11.4° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$ solution) 3605 (w sharp), 3400 (w br), 2970 (s), 2930 (s), 2875 (m), 1702 (vs); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.37 (5H, m, Ar*H*), 5.42 (1H, t, *J* = 7.0 Hz, C=C*H*Et), 4.46 & 4.52 (2H, AB_q, J_{AB} = 12.0 Hz, CH_2Ph), 4.12 (1H, dd, *J* = 9.0, 2.8 Hz, C*H*OH), 3.67 (1H, t, *J* = 8.7 Hz, C*H*OBn), 3.46 (1H, dd, *J* = 8.9, 5.1 Hz, C*H*OBn), 3.08 (1H, dqd, *J* = 8.7, 7.1, 5.1 Hz, CCH_3HCH_2OBn), 2.90 (1H, dq, *J* = 9.0, 7.1 Hz, $COHCHCH_3$), 2.56 (1H, d, *J* = 2.8 Hz, O*H*), 2.04 (2H, qd, *J* = 7.5, 7.5 Hz, CH_3CH_2), 1.61 (3H, s, CH_3C=), 1.06 (3H, d, *J* = 7.1 Hz, CH_3), 0.97 (3H, t, *J* = 7.5 Hz, CH_3CH_2), 0.92 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.4, 137.8, 133.6, 131.2, 128.3, 127.6, 127.57, 80.1, 73.3, 72.2, 49.2,

46.1, 20.8, 13.9, 13.7, 13.4, 10.6; m/z (CI^+, NH_3) 322 (4, MH^++NH_3), 287 (100, MH^+–H_2O), 207 (30), 108 (45); HRMS (CI, NH_3) Calcd for $C_{19}H_{32}O_3N$ (MH^++NH_3) 322.2382. Found 322.2382.

Reduction of di-*n*-butylboron aldolate 23a. To a stirred solution of aldol product **13** (60 mg, 0.2 mmol) at –78 °C in dry THF (4 ml) and MeOH (1 ml) was added di-*n*-butylmethoxyborane (88.3 µl, 2.9 M, 0.25 mmol). After stirring at this temperature for 15 min, lithium borohydride (0.25 ml, 2 M, 0.5 mmol) was added and stirring was continued for 1h. The reaction mixture was quenched by the addition of pH7 buffer (1.5 ml) and MeOH (1.5 ml), followed by the addition of H_2O_2 (0.4 ml, 30%), and allowed to warm to room temperature with stirring for 1 h. The mixture was then partitioned between EtOAc (3 x 15 ml) and water (10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography gave an oil (42 mg, 70%), which was shown by ^1H NMR to be an *ca.* 60:40 mixture of diol isomers: R_f 0.37 (10% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.37 (10H, m, Ar*H*), 5.40 (1H, t, *J* = 7.0 Hz, C=C*H*Et), 5.33 (1H, t, *J* = 6.9 Hz, C=C*H*Et), 4.52 (4H, s, 2 x CH_2Ph), 4.13 (2H, br s, O*H*), 3.98 (1H, d, *J* = 10.0 Hz, C*H*OH), 3.90 (2H, d, *J* = 9.2 Hz, 2 x C*H*OH), 3.84 (1H, d, *J* = 9.2 Hz, C*H*OH), 3.55-3.60 (5H, m, includes O*H*), 3.35-3.40 (1H, m), 1.90-2.10 (6H, m), 1.65-1.80 (2H, m, $CHCH_3$), 1.60 (3H, s, CH_3C=), 1.58 (3H, s, CH_3C=), 0.99 (3H, d, *J* = 7.0 Hz, CH_3), 0.95 (6H, t, *J* = 7.5 Hz, 2 x CH_3CH_2), 0.85 (3H, d, *J* = 6.9 Hz, CH_3), 0.72 (3H, d, *J* = 6.7 Hz, CH_3), 0.59 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 135.1, 130.8, 128.4, 128.3, 127.7, 127.6, 127.5, 85.2, 84.9 (epi), 79.5, 76.4 (epi), 75.4, 73.4, 73.1 (epi), 72.7 (epi), 37.7, 35.2, 34.9 (epi), 34.3 (epi), 20.8 (epi), 20.6, 13.8 (2 C), 13.2, 12.1 (epi), 10.3, 10.1 (epi), 9.2, 8.8 (epi). NB: the resonances marked *epi* are those assigned to the anti reduction product **24**, the other resonances are identical to those recorded for the pure syn reduction product **22** (there is some overlap of signals in the aromatic region).

(2*R*,3*S*,4*S*,5*S*,6*E*)-2,4,6-Trimethyl-1-phenylmethoxy-6-nonene-3,5-diol (22). To a stirred solution of dicyclohexylboron chloride (2.4 ml, 11 mmol) in dry Et_2O (20 ml) was added Et_3N (1.6 ml, 11 mmol) and the mixture was cooled to –15 °C. A solution of the ketone (*R*)-**9** (1.54 g, 7.5 mmol) in Et_2O (5 ml) was added *via* cannula and the mixture stirred for 2 h at –15 °C. A solution of (*E*)-2-methyl-2-pentenal (**14**) (1.5 ml, 13.1 mmol) in Et_2O (5 ml) was added *via* cannula and stirring was continued at this temperature for 2 h. The reaction mixture was then cooled to –78 °C and $LiBH_4$ (19.2 ml, 2 M, 38 mmol) was added. After 2 h, the reaction mixture was partitioned between Et_2O (3 x 100 ml) and saturated aqueous NH_4Cl solution (60 ml), the organic extracts were combined and washed with saturated aqueous NaCl solution then concentrated *in vacuo* to give an oil. For optimum yield and ease of isolation, the boronate was best purified by flash chromatography prior to oxidative removal of the boron. Purification of this oil by flash chromatography (CH_2Cl_2) gave the semi-pure aldolate (4.3 g). This residue was suspended in MeOH (30 ml), 10% NaOH (10 ml) was added and the mixture cooled to 0 °C. Hydrogen peroxide (15 ml; 30% aqueous) was added dropwise and stirring was continued at room temperature for 2 h. The mixture was then poured into water (150 ml) and extracted with CH_2Cl_2 (3 x 150 ml). The combined organic extracts were washed in turn with saturated $NaHCO_3$ (50 ml), saturated $NaHSO_3$ (50 ml), brine (50 ml), then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (10% Et_2O/CH_2Cl_2) gave the syn diol **22** (1.85 g, 81%) as a colourless solid: mp 64–65 °C (pentane); R_f 0.37 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$+15.6° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3440 (s br), 2970 (vs), 2930 (s), 2870 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.37 (5 H, m, Ar*H*), 5.33 (1H, t, *J* = 6.9 Hz, C=C*H*Et), 4.52 (2H, s, CH_2Ph), 4.16 (1H, s, O*H*), 4.08 (1H, s, O*H*), 3.90 (1H, d, *J* = 9.2 Hz, C*H*OH), 3.84 (1H, d, *J* = 9.2 Hz, C*H*OH), 3.55-3.60 (2H, m), 2.02 (2H, qd, *J* = 7.5, 6.9 Hz, CH_3CH_2), 1.92-1.97 (1H, m, $CHCH_3$), 1.72-1.79 (1H, m, $CHCH_3$), 1.60 (3H, s, CH_3C=), 0.99 (3H, d, *J* = 7.0 Hz, CH_3), 0.95 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.59 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 135.1, 130.8, 128.3, 127.6, 127.5, 85.2, 79.5, 75.4, 73.4, 37.7, 35.2, 20.6, 13.8, 13.2, 10.3, 9.2; m/z (CI^+, NH_3) 307 (3, MH^+), 290 (20), 289 (100, MH^+–H_2O), 181 (50); HRMS (CI,

NH_3) Calcd for $C_{19}H_{31}O_3$ ($M+H^+$) 307.2273. Found 307.2273; Anal. Calcd for $C_{19}H_{30}O_3$: C 74.47, H 9.87. Found C 74.58, H 9.90.

(2*R*,3*S*,4*S*,5*S*,6*E*)-2,4,6-Trimethyl-3,5-[[bis-dimethyl-methylene]dioxy]-1-[(phenylmethoxy)methyl]-6-nonene. To a stirred solution of diol **22** (0.1 g, 0.33 mmol) in CH_2Cl_2 (1 ml) was added 2,2-dimethoxypropane (1.0 ml), followed by pyridinium-*p*-toluenesulphonate (~10 mg) and stirring was continued for 3 h. The solvent was then removed *in vacuo* and the residue purified by flash chromatography (CH_2Cl_2) to give the acetonide of **22** (60 mg, 53%): R_f 0.8 (CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.35 (5H, m, Ar*H*), 5.41 (1H, t, *J* = 5.7 Hz, C=C*H*Et), 4.49 & 4.53 (2H, AB_q, J_{AB} = 12.0 Hz, CH_2Ph), 3.82 (1H, d, *J* = 10.2 Hz, C*H*OC(CH_3)$_2$), 3.75 (1H, dd, *J* = 10.3, 2.1 Hz, C*H*OC(CH_3)$_2$), 3.49 (1H, dd, *J* = 8.8, 8.5 Hz, C*H*OBn), 3.32 (1H, dd, *J* = 8.8, 6.2 Hz, C*H*OBn), 2.0-2.1 (3H, m), 1.6-1.75 (1H, m, C*H*CH_3), 1.63 (3H, s, CH_3C=), 1.43 (3H, s, C(CH_3)CH_3), 1.36 (3H, s, C(CH_3)CH_3), 0.98 (3H, t, *J* = 7.5 Hz, CH_3CH_2), 0.89 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.64 (3H, d, *J* = 6.7 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 132.5, 132.2, 128.3, 127.5, 127.4, 97.8, 82.3, 73.1, 73.0, 34.2, 32.1, 30.1, 20.9, 19.8, 13.9, 11.5, 11.0, 9.5.

(2*R*,3*S*,4*S*,5*S*,6*E*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-1-phenylmethoxy-6-nonene (25). To a stirred solution of diol **22** (1.5 g, 4.9 mmol) in dry CH_2Cl_2 (5 ml) was added 2,6-lutidine (2 ml, 17.2 mmol), followed by di-*tert*-butylsilyl bis-(trifluoromethanesulfonate) (2.45 ml, 7.6 mmol). After stirring for 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (250 ml) and was successively washed with saturated $NaHCO_3$ (50 ml), $NaHSO_4$ (0.3 M, 2 x 50 ml) and brine (50 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2) to give **25** (1.98 g, 90 %) as a colourless oil: R_f 0.8 (CH_2Cl_2); $[\alpha]_D^{20}$ –9.5° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 2965 (s), 2930 (s), 2960 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.37 (5H, m, Ar*H*), 5.30 (1H, t, *J* = 6.8 Hz, C=C*H*Et), 4.48 & 4.54 (2 H, AB_q, J_{AB} = 11.7 Hz, CH_2Ph), 4.06 (1H, d, *J* = 9.6 Hz, C*H*OSi), 4.04 (1H, dd, *J* = 8.2, 1.7 Hz, C*H*OSi), 3.60 (1 H, dd, *J* = 8.6, 8.5 Hz, CH*H*OBn), 3.36 (1 H, dd, *J* = 8.6, 5.9 Hz, CH*H*OBn), 2.00-2.10 (3H, m), 1.75-1.85 (1H, m, C*H*CH_3), 1.62 (3H, s, CH_3C=), 1.03 (9H, s, Si^{t}Bu), 1.02 (9H, s, Si^{t}Bu), 0.96 (3H, t, *J* = 7.5 Hz, CH_3CH_2), 0.87 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.59 (3H, d, *J* = 6.8 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 135.1, 130.7, 128.3, 127.7, 127.4, 87.5, 77.9, 73.5, 73.3, 37.4, 36.1, 27.8, 27.4, 23.1, 20.8, 20.4, 14.0, 12.9, 10.5, 9.2; m/z (CI^+, NH_3) 447 (40, MH^+), 299 (15), 102 (100), 91 (30); HRMS (CI, NH_3) Calcd for $C_{27}H_{47}O_3Si$ ($M+H^+$) 447.3294. Found 447.3294.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-1-phenylmethoxy-7-nonanol (20). To a stirred solution of the alkene **25** (1.9 g, 4.25 mmol) in dry THF (20 ml) was added dropwise BH_3•SMe_2 (10 M, 1.7 ml, 17 mmol). After stirring for 16 h at room temperature, the reaction mixture was cooled in an ice/salt bath and H_2O_2 (30%, 20 ml) was added with care (NB: reaction of peroxide with excess BH_3 is exothermic and the addition must be very slow at first), followed by 10% NaOH (20 ml). The reaction mixture was then allowed to warmed to room temperature and stirring was continued for 2 h. The mixture was then diluted with H_2O (250 ml) and extracted with EtOAc (3 x 150 ml). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ (50 ml), saturated aqueous $NaHSO_3$ (50 ml) and brine (50 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF/10% NaOH (1:1, 35 ml) and stirred for 24 h. This mixture was then diluted with water (200 ml), extracted with EtOAc (3 x 150 ml), and the organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash chromatography (10% Et_2O/CH_2Cl_2) gave alcohol **20** as a colourless oil (1.68 g, 85%). Alternatively, the crude reaction product may be used in the subsequent hydrogenation with the same overall yield. R_f 0.6 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –10.4° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3475 (w br), 2965 (s), 2930 (s),

2860 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.34 (5H, m, Ar*H*), 4.53 & 4.47 (2H, AB_q, J_{AB} = 11.8 Hz, C*H*$_2$Ph), 3.97 (1H, dd, *J* = 9.8, 1.8 Hz, C*H*OSi), 3.81 (1H, dd, *J* = 9.8, 2.2 Hz, C*H*OSi), 3.68 (1H, m, C*H*OH), 3.58 (1H, t, *J* = 8.5 Hz, C*H*HOBn), 3.34 (1H, dd, *J* = 8.5, 5.9 Hz, C*H*HOBn), 2.32 (1H, br s, O*H*), 2.02-2.13 (2H, m), 1.92 (1H, qdd, *J* = 6.9, 6.2, 2.3 Hz, C*H*CH$_3$), 1.70 (1H, dqd, *J* = 15.0, 7.5, 2.8 Hz, C*H*CH$_3$), 1.37-1.47 (1H, m), 1.03 (3H, d, *J* = 7 Hz, CH$_3$), 1.02 (9H, s, Si^{t}Bu), 0.99 (9H, s, Si^{t}Bu), 0.97 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_3$), 0.85 (3H, d, *J* = 6.8 Hz, CH$_3$), 0.79 (3H, d, *J* = 6.8 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 128.3, 127.6, 127.4, 85.3, 79.3, 74.5, 73.4, 73.3, 40.2, 39.7, 35.9, 28.0, 27.9, 27.3, 23.2, 20.1, 16.3, 12.4, 10.2, 9.3; m/z (CI$^+$, NH_3) 465 (100, MH$^+$), 447 (5); HRMS (CI, NH_3) Calcd for $C_{27}H_{49}O_4Si$ (M+H$^+$) 465.3400. Found 465.3400.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-1,7-nonandiol (27). To a stirred solution of the benzyl ether **20** (1.5 g, 3.2 mmol) in EtOH (30 ml) was added 10% Pd/C (0.6 g) and the mixture was stirred under a hydrogen atmosphere for 5 h. The catalyst was then removed by filtration through celite and the solvent concentrated *in vacuo* to give a colourless oil. Purification by flash chromatography (10% Et_2O/CH_2Cl_2) gave the alcohol **27** as a white solid (1.21 g, 100%): mp 95–96 °C (pentane); R_f 0.15 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$–2.7° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3620 (w sh), 3490 (m br), 2965 (s), 2930 (s), 2860 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (1H, dd, *J* = 9.8, 2.1 Hz, C*H*OSi), 3.77-3.83 (1H, m), 3.80 (1H, dd, *J* = 9.8, 2.0 Hz, C*H*OSi), 3.64-3.74 (2H, m, C*H*OH), 2.70 (1H, br d, *J* = 6.6 Hz, O*H*), 2.07-2.17 (2H, m, C*H*CH$_3$ & O*H*), 1.82-1.95 (2H, m, 2 x C*H*CH$_3$), 1.68 (1H, dqd, *J* = 13, 7.0, 2.7 Hz, CH*H*CH$_3$), 1.40 (1H, dqd, *J* = 13, 7.0, 7.0 Hz, CH*H*CH$_3$), 0.95-1.05 (24H, m, 2 x Si^{t}Bu & 2 x CH$_3$), 0.96 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_3$), 0.78 (3H, d, *J* = 6.7 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 84.9, 84.1, 74.0, 68.1, 40.3, 39.7, 36.5, 28.0, 27.9, 27.2, 23.1, 20.2, 16.0, 12.5, 10.0, 8.7; m/z (CI$^+$, NH_3) 375 (100, MH$^+$); HRMS (CI, NH_3) Calcd for $C_{20}H_{43}O_4Si$ (M+H$^+$) 375.2931. Found 375.2931; Anal. Calcd for $C_{20}H_{42}O_4Si$: C 64.12, H 11.30. Found C 64.21, H 11.43.

(2*S*,3*R*,4*S*,5*S*,6*S*)-2,4,6-Trimethyl-3,5-[[bis(1,1-dimethylethyl)-silylene]dioxy]-7-keto-non-anal (28). To a stirred solution of the diol **27** (0.3 g, 0.8 mmol) in CH_2Cl_2 (10 ml) at room temperature was added PCC (0.75 g, 3.5 mmol) and the mixture was stirred for 3 h. The reaction mixture was then diluted with dry Et_2O (20 ml) and the resulting black gum triturated until it became a granular solid. Filtration of the mixture through florisil (which had been wet with Et_2O), eluting with Et_2O, followed by concentration *in vacuo* gave the ketoaldehyde **28** as a colourless oil (0.28 g, 95%). This compound was unstable to silica gel chromatography. It was found to be ≥98% pure by ^{1}H and ^{13}C NMR and was used without further purification in the next step. R_f 0.41 (2.5% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$–12.8° (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.71 (1H, s, C*H*=O), 4.41 (1H, dd, *J* = 9.9, 2.2 Hz, C*H*OSi), 3.95 (1H, dd, *J* = 9.8, 2.6 Hz, C*H*OSi), 2.75 (qd, *J* = 7.1, 2.6 Hz, C*H*CH$_3$C=O), 2.60 (1H, dq, *J* = 18.7, 7.1 Hz, CH$_3$CH*H*C=O), 2.43-2.55 (2H, m, CH$_3$CH*H*C=O & C*H*CH$_3$C=O), 1.88 (1H, ddq, *J* = 9.9, 9.8, 6.7 Hz, C(OSi)C*H*CH$_3$C(OSi)), 1.33 (3H, d, *J* = 7.1 Hz, CH$_3$), 1.11 (3H, d, *J* = 6.9 Hz, CH$_3$), 0.99 (9H, s, Si^{t}Bu), 0.99 (3H, t, *J* = 7.1 Hz, CH$_2$CH$_3$), 0.90 (9H, s, Si^{t}Bu), 0.84 (3H, d, *J* = 6.7 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.3, 204.5, 82.7, 78.7, 49.6, 49.3, 38.3, 35.0, 27.8, 26.9, 23.1, 20.0, 14.3, 12.5, 7.3, 6.0; m/z (CI$^+$, NH_3) 371 (100, MH$^+$), 357 (30); HRMS (CI, NH_3) Calcd for $C_{20}H_{39}O_4Si$ (M+H$^+$) 371.2618. Found 371.2618.

(3*S*,4*R*,5*S*,6*S*,7*S*,8*S*)-3-Hydroxy-4,6,8-trimethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]-dioxy]-undecan-9-one (26) and (3*R*,4*R*,5*S*,6*S*,7*S*,8*S*)-3-hydroxy-4,6,8-trimethyl-5,7-[[bis-(1,1-dimethylethyl)-silylene]dioxy]-undecan-9-one (29). To a stirred solution of aldehyde **28** (0.15 g, 0.405 mmol) in Et_2O (40 ml) at –100 °C was added dropwise a solution of EtMgBr (3.5 ml, 0.8 M in Et_2O, 2.8 mmol) and this mixture was allowed to warm to –50 °C over 15 min. After a further 15 min, the reaction mixture was quenched by the addition of MeOH (0.5 ml), followed by saturated aqueous NH_4Cl solution (20

ml). The aqueous layer was separated and further extracted with Et_2O (3 x 15 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was purified by flash chromatography (2.5% Et_2O/CH_2Cl_2) to give **26** (0.12 g, 74%) and its epimer **29** (20 mg, 12%). The major isomer **26** (assumed to be 3*S*) had mp 58–59 °C (pentane); R_f 0.31 (2.5% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –16.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3490 (m br), 2970 (s), 2930 (s), 2860 (m), 1700 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.01 (1H, dd, *J* = 9.8, 2.1 Hz, C*H*OSi), 3.91 (1H, dd, *J* = 9.7, 2.8 Hz, C*H*OSi), 3.84 (1H, s, O*H*), 3.75 (1H, ddd, *J* = 7.5, 5.7, 1.7 Hz, C*H*OH), 2.75 (1H, qd, *J* = 7.1, 2.8 Hz, C*H*(CH_3)C=O), 2.59 (1H, dq, *J* = 18.7, 7.2 Hz, C=OCH*H*CH_3), 2.49 (1H, dq, *J* = 18.7, 7.2 Hz, C=OCH*H*CH_3), 1.89 (1H, ddq, *J* = 9.8, 9.7, 6.7 Hz, C(OSi)C*H*CH_3C(OSi)), 1.71 (1H, qdd, *J* = 7.0, 1.7, 1.7 Hz, C*H*CH_3), 1.58 (1H, ddq, *J* = 13.7, 7.5, 7.5 Hz, CHOHCH*H*CH_3), 1.37 (1H, dqd, *J* = 13.7, 7.5, 5.7 Hz, CHOHCH*H*CH_3), 1.31 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 1.04 (9H, s, Si^{t}Bu), 0.99 (3H, t, *J* = 7.2 Hz, C=OCH$_2$C*H*$_3$), 0.94 (9H, s, Si^{t}Bu), 0.92 (3H, t, *J* = 7.5 Hz, CHOHCH$_2$C*H*$_3$), 0.90 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.80 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.2, 86.8, 82.7, 78.4, 49.7, 38.9, 37.7, 35.0, 27.8, 27.7, 26.9, 23.1, 20.1, 14.2, 12.5, 10.6, 7.3, 4.4; m/z (CI^+, NH_3) 401 (100, MH^+), 383 (15), 357 (15), 313 (20), 299 (20), 285 (20), 257 (18), 215 (40); HRMS (CI, NH_3) Calcd for $C_{22}H_{45}O_4Si$ ($M+H^+$) 401.3087. Found 401.3087; Anal. Calcd for $C_{22}H_{44}O_4Si$: C 65.95, H 11.07. Found C 66.08, H 10.96.

The minor isomer **29** had mp 45–46 °C (pentane); R_f 0.26 (2.5% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –10.7° (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) 3492 (w br), 2968 (s), 2935 (s), 2860 (s), 1699 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.19 (1H, dd, *J* = 9.8, 2.1 Hz, C*H*OSi), 3.91 (1H, dd, *J* = 9.7, 2.7 Hz, C*H*OSi), 3.44 (1H, dddd, *J* = 8.2, 8.2, 5.1, 5.1 Hz, C*H*OH), 3.11 (1H, d, *J* = 8.2 Hz, O*H*), 2.75 (1H, qd, *J* = 7.1, 2.7 Hz, C*H*(CH_3)C=O), 2.60 (1H, dq, *J* = 18.7, 7.2 Hz, C=OCH*H*CH_3) 2.48 (1H, dq, *J* = 18.7, 7.2 Hz, C=OCH*H*CH_3), 1.89 (1H, ddq, *J* = 9.8, 9.7, 6.7 Hz, C(OSi)C*H*CH_3C(OSi)), 1.73 (1H, qdd, *J* = 7.0, 5.1, 2.1 Hz, CH(OSi)C*H*CH_3), 1.50-1.65 (2H, m, CHOHCH_2CH$_3$), 1.30 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 1.03 (9H, s, Si^{t}Bu), 1.02 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 0.99 (3H, t, *J* = 7.2 Hz, C=OCH$_2$C*H*$_3$), 0.96 (3H, t, *J* = 7.5 Hz, CHOHCH$_2$C*H*$_3$), 0.94 (9H, s, Si^{t}Bu), 0.77 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.3, 82.7, 80.4, 77.6, 49.7, 38.7, 37.6, 35.0, 28.8, 27.8, 27.0, 23.0, 20.1, 14.2, 12.4, 10.7, 10.6, 7.3.

(4*S*,5*R*,6*R*,7*S*,8*S*)-4,6,8-Trimethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-3,9-undecandione (30). To a stirred solution of a 1:1 mixture of the alcohols **26** and **29** (14 mg, 0.035 mmol) in CH_2Cl_2 (4 ml) was added PCC (40 mg, 0.18 mmol) and the mixture was stirred for 18 h. The reaction mixture was diluted with dry Et_2O (10 ml) and the resulting black gum triturated until it became a granular solid. Filtration of this mixture through florisil (which had been wet with Et_2O), eluting with Et_2O, followed by concentration *in vacuo* gave the crude diketone as an oil. Purification by flash chromatography (2.5% Et_2O/CH_2Cl_2) gave diketone **30** (11 mg, 79%) as a white solid: mp 58–59 °C (pentane); R_f 0.53 (5% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –33.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2970 (s), 2935 (s), 2860 (m), 1700 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.26 (1H, dd, *J* = 9.9, 2.6 Hz, C*H*OSi), 3.91 (1H, dd, *J* = 9.7, 2.6 Hz, C*H*OSi), 2.74 (1H, qd, *J* = 7.1, 2.6 Hz, C*H*(CH_3)C=O), 2.43-2.65 (5H, m, 5 x C=OC*H*), 1.82 (1H, ddq, *J* = 9.9, 9.7, 6.7 Hz, C(OSi)C*H*CH_3C(OSi)), 1.31 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 1.11 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 1.02 (3H, t, *J* = 7.2 Hz, C=OCH$_2$C*H*$_3$), 0.99 (3H, t, *J* = 7.2 Hz, C=OCH$_2$C*H*$_3$), 0.96 (9H, s, Si^{t}Bu), 0.92 (9H, s, Si^{t}Bu), 0.83 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.4, 213.2, 82.7, 80.5, 49.7, 49.6, 38.8, 35.0, 33.4, 27.7, 27.0, 23.1, 20.0, 14.3, 12.6, 7.9, 7.7, 7.3; m/z (CI^+, NH_3) 399 (100, MH^+), 341 (20), 313 (60), 255 (95), 215 (40); HRMS (CI, NH_3) Calcd for $C_{22}H_{43}O_4Si$ ($M+H^+$) 399.2931. Found 399.2930; Anal. Calcd for $C_{22}H_{42}O_4Si$: C 66.28, H 10.62. Found C 66.50, H 10.81.

2-Methylpent-1-en-3-ol *rac*-(16). To a stirred solution of methacrolein (20.4 ml, 0.25 mol) in Et_2O (100 ml) at –78 °C was added EtMgBr (250 ml, 1.0 M in Et_2O, 0.25 mol) *via* cannula over 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 ml), extracted with Et_2O (3 x 100 ml), then

dried ($MgSO_4$) and concentrated *in vacuo*. Distillation under reduced pressure (bp 46–49 °C, 20 mmHg) gave *rac*-**16** as a colourless liquid (16.8 g, 68%): R_f 0.39 (10% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.91 (1H, br s, C=CH*H*), 4.82 (1H, br s, C=CH*H*), 3.97 (1H, br t, *J* = 7.0 Hz, C*H*OH), 1.69 (3H, s, CH_3C=C), 1.63 (1H, s, O*H*), 1.48-1.61 (2H, m, CH_2CH_3), 0.87 (3H, t, *J* = 7.5 Hz, CH_2CH_3).

Sharpless kinetic resolution giving (3*S*)-2-Methylpent-1-en-3-ol (16). To a stirred solution of *rac*-**16** (8.12 g, 81.1 mmol) in dry CH_2Cl_2 (300 ml) was added *D*-(–)-diisopropyl tartrate (2.6 ml, 12.2 mmol) and powdered molecular sieves (2.5 g). The reaction mixture was then cooled to –18 °C and $Ti(O^iPr)_4$ (2.35 ml, 7.9 mmol) was added. After 30 min, *tert*-butyl hydroperoxide (8.5 ml, 5.5 M in isooctane, 46.7 mmol) was added and stirring was continued for 3 h. The reaction mixture was then stored in the freezer (–20 °C) for 48 h. The reaction mixture was quenched by addition of a precooled (0 °C) $FeSO_4$/citric acid solution (33 g $FeSO_4$ and 11 g citric acid in 100 ml H_2O) with vigorous stirring for 40 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of tartrate, epoxide and resolved alcohol. Purification by flash chromatography (5% Et_2O/CH_2Cl_2) gave the resolved alkene (*S*)-**16** as a colourless liquid (3.0 g, 74% based on *S*-enantiomer): $[\alpha]_D^{20}$–5.6° (*c* 1.6, $CHCl_3$). MTPA ester analysis of this alcohol indicated ≥98 % ee.

[(3*S*)-2-Methyl-1-penten-3-yl] propionate (15). To a stirred solution of the alcohol (*S*)-**16** (2.8 g, 28 mmol) in CH_2Cl_2 (100 ml) was added dry pyridine (3.16 ml, 39 mmol), followed by propionyl chloride (3.4 ml, 39 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (200 ml), washed with HCl (1 M, 2 x 100 ml) and saturated aqueous $NaHCO_3$ (100 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residue (50 °C, 10 mmHg) gave the ester **15** (3.5 g, 80%): R_f 0.39 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$–28.2° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3025 (m), 2975 (s), 2935 (s), 2942 (m), 2880 (m), 1816 (m), 1725 (vs); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.07 (1H, t, *J* = 6.7 Hz, C*H*OR), 4.89 (1H, br s, C=CH*H*), 4.84 (1H, br s, C=CH*H*), 2.30 (1H, q, *J* = 7.5 Hz, CH_3CH_2C=O), 1.67 (3H, s, CH_3C=C) 1.55-1.65 (2H, m, CH(OR)CH_2CH_3), 1.11 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.83 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 143.0, 112.5, 78.2, 27.7, 25.5, 18.0, 9.5, 9.1.

(2*R*,4*E*)-2,4-Dimethylhept-4-enoic acid (31). Dry triethylamine (4 ml) was added to chlorotrimethylsilane (4 ml) followed by centrifuging to separate off the gelatinous white precipitate of amine hydrochloride. To a stirred solution of **15** (0.8 g, 5.1 mmol) in THF (50 ml) at –78 °C was added the above TMSCl/Et_3N solution (6.6 ml of clear supernatant, 26 mmol TMSCl, 24 mmol Et_3N), followed by a solution of lithium diisopropylamide (4.7 ml, 1.4 M, 6.6 mmol) in THF. The reaction mixture was stirred at –78 °C for 1 h, allowed to warm slowly to room temperature, stirred for 1h, and then heated to reflux for 4 h. The reaction mixture was then quenched by the addition of HCl solution (1 M, 30 ml) and then stirred for 40 min. The mixture was then basified by the addition of NaOH (10%), washed with ether (3 x 80 ml), acidified (H_2SO_4, 3 M), and extracted into Et_2O (3 x 80 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude acid **31** (0.58 g, 72%). This acid was generally not purified further and used in the subsequent reduction. R_f 0.2 (10% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 11.50 (1H, br s, C=OO*H*), 5.17 (1H, br t, *J* = 7.0 Hz, EtC*H*C=C), 2.60 (1H, sextet, *J* = 7.0 Hz, C*H*CH_3COOH), 2.38 (1H, dd, *J* = 13.5, 6.9 Hz), 1.92-2.08 (3H, m), 1.57 (3H, s, CH_3C=C), 1.10 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.91 (3H, t, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.2, 131.0, 129.4, 43.6, 37.8, 21.2, 16.2, 15.4, 14.2.

(2*R*,4*E*)-2,4-Dimethylhept-4-en-1-ol. To a stirred solution of lithium aluminium hydride (0.55 g, 14.5 mmol) in Et_2O (40 ml) at –78 °C was added the acid **31** (0.52 g, 3.3 mmol). The resulting mixture was allowed to warm slowly to 0 °C and stirred at this temperature for 30 min. The reaction mixture was quenched by the

addition of dilute H_2SO_4 (1 M, 50 ml). The mixture was then extracted with Et_2O (3 x 50 ml), the combined organic layers washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (10% Et_2O/CH_2Cl_2) gave (2*R*,4*E*)-2,4-dimethylhept-4-en-1-ol (0.36 g, 76%) as a colourless oil: R_f 0.38 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ +5.1° (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3625 (m), 3010 (m), 2961 (s), 2929 (s), 2870 (m), 1601 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.15 (1H, br t, *J* = 7.1 Hz, EtC*H*C=C), 3.47 (1H, dd, *J* = 10.6, 5.7 Hz, C*H*HOH), 3.40 (1H, dd, *J* = 10.6, 5.9 Hz, C*H*HOH), 1.93-2.03 (3H, m), 1.7-1.86 (3H, m, includes OH), 1.58 (3H, s, CH_3C=C), 0.92 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.85 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.0, 128.3, 68.5, 44.3, 33.5, 21.1, 16.7, 15.7, 14.3; m/z (CI^+, NH_3) 160 (20, MH^++NH_3), 143 (100, MH^+); HRMS (CI, NH_3) Calcd for $C_9H_{18}O$ ($M+H^+$) 142.1358. Found 142.1358. MTPA ester analysis of this alcohol revealed it to be 80 % ee. A sample of this alcohol was oxidised to the aldehyde (*R*)-**8** and reduced back by $LiAlH_4$, which had the same enantiomeric excess indicating no racemisation in this process.

(2*R*,4*E*)-2,4-Dimethylhept-4-enal (8). To a stirred solution of (2*R*,4*E*)-2,4-dimethylhept-4-en-1-ol (0.17 g, 1.2 mmol) in CH_2Cl_2 (7 ml) was added pyridinium chlorochromate (0.45 g, 2.1 mmol). After 3 h, the reaction mixture was diluted with dry Et_2O (20 ml) and the resulting black gum triturated until it became a granular solid. Filtration of the mixture through florisil (which had been wet with Et_2O), eluting with Et_2O, followed by concentration *in vacuo* gave the crude aldehyde. Purification by flash chromatography (CH_2Cl_2) gave the aldehyde (*R*)-**8** (0.13 g, 77%) as an oil, which was formed in 80% ee. This compound deteriorated on storage and was best used immediately in the subsequent step. R_f 0.59 (CH_2Cl_2); $[\alpha]_D^{20}$ –9.6 ° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3024 (m), 2965 (s), 2932 (s), 2873 (m), 1720 (vs); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.59 (1H, d, *J* = 2.0 Hz, C=O*H*), 5.16 (1H, br t, *J* = 7.0 Hz, EtC*H*C=C), 2.47 (1H, sextet, *J* = ~6.7.Hz, C*H*(CH_3)CH=O), 2.39 (1H, dd, *J* = 13.6, 6.6 Hz, C*H*HCH(CH_3)CH=O), 1.90-2.00 (3H, m), 1.57 (3H, s, CH_3C=C), 1.01 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.91 (3H, t, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.3, 130.6, 129.5, 44.3, 40.7, 21.2, 15.6, 14.2, 13.1.

(3*S*,4*R*,5*S*,6*S*,7*S*,8*S*,10*R*,11*S*,12*R*)-3,11-Dihydroxy-4,6,8,10,12,14-hexamethyl-5,7-[[bis-(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-9-one (38) and (3*S*,4*R*,5*S*,6*S*,7*S*,8*S*, 10*R*,11*S*,12*S*)-3,11-Dihydroxy-4,6,8,10,12,14-hexamethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-9-one (37). To a stirred solution of ketone **26** (95 mg, 0.24 mmol) in dry CH_2Cl_2 (7 ml) at –78 °C was added dropwise $TiCl_4$ (0.71 ml, 1.0 M CH_2Cl_2, 0.71 mmol), giving after 30 min a pale yellow solution (a viscous residue is formed initially, which becomes homogeneous upon stirring). Diisopropylethylamine (89 µl, 0.51 mmol) was then added dropwise and stirring was continued for 1 h. A solution of the aldehyde (*R*)-**8** (0.10 g, 0.71 mmol) in CH_2Cl_2 (2.5 ml) was then added *via* cannula. The resulting mixture was stirred at –78 °C for 30 min and then warmed to –5 °C for 5 min. The reaction mixture was quenched by the addition of pH7 buffer (15 ml) and extracted with Et_2O (3 x 20 ml). The combined organic layers were washed with saturated brine (15 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (30% Et_2O/30-40 petrol) gave aldol adduct **38** (96 mg, 75 %), along with the adduct **37** (19 mg, 15%) formed from the enantiomeric aldehyde. The major isomer **38** had R_f 0.2 (30% Et_2O/30-40 petrol); $[\alpha]_D^{20}$ +21.7° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3490 (m br), 2965 (s), 2930 (s), 2860 (m), 1690 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.11 (1H, t, *J* = 6.9 Hz, *H*C=C), 4.04 (1H, dd, *J* = 9.8, 3.8 Hz, C*H*OSi), 4.02 (1H, dd, *J* = 9.7, 1.9 Hz, C*H*OSi), 3.81 (1H, s, C_3-O*H*), 3.76 (1H, br t, *J* = 6.1 Hz, C_3-*H*), 3.57 (1H, dt, *J* = 7.5, 2.6 Hz, C_{11}-*H*), 3.03 (1H, d, *J* = 2.6 Hz, C_{11}-O*H*), 2.90-3.00 (2H, m, C_{10}-*H* & C_8-*H*),1.9-2.05 (4H, m, C_{13}-*H* & C_{16}-*H*), 1.65-1.75 (2H, m), 1.55-1.65 (2H, m), 1.54 (3H, s, C=C(CH_3)), 1.32-1.42 (1H, m), 1.23 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.13 (3H, d, *J* = 7.1 Hz, CHCH_3), 1.03 (9H, s, Si^{t}Bu), 0.98 (9H, s, Si^{t}Bu), 0.93 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.92 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.91 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.88 (3H, d, *J* = 6.4 Hz, CHCH_3), 0.74 (3H, d, *J* = 6.6 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 217.3, 132.0, 128.8, 86.5, 81.3, 78.3, 74.5, 50.2, 48.6, 43.5, 39.3, 37.7, 33.2, 27.7 (2C), 27.1, 23.1, 21.2, 20.1, 15.4, 15.3, 14.3, 13.7, 12.7, 10.6, 10.0, 4.4; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.24 (1H, t, *J* = 6.9 Hz, *H*C=C), 3.96 (1H, dd, *J* = 9.8, 3.8 Hz, C*H*OSi), 3.91 (1H, dd, *J* = 9.7, 1.9 Hz, C*H*OSi), 3.79 (1H, br t, *J* = 6.5 Hz, C*H*OH), 3.75 (1H, dt, *J* = 7.5, 3.5 Hz, C*H*OH), 3.55 (1H, s, O*H*), 2.89 (1H, qd, *J* = 7.1, 3.8 Hz, C*H*(CH_3)C=O), 2.80 (1H, d, *J* = 3.2 Hz, O*H*), 2.76 (1H, qd, *J* = 7.0, 3.8 Hz, C*H*(CH_3)C=O), 2.12 (1H, dd, *J* = 12.8, 3.9 Hz, C=C(CH_3)-C*H*H), 1.93-2.03 (3H, m), 1.50-1.87 (4H, m), 1.55 (3H, s, C=C(CH_3)), 1.32-1.44 (1H, m), 1.14 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.10 (6H, d, *J* = 6.7 Hz, 2 x CHCH_3), 1.09 (3H, t, *J* = 7.0 Hz, CH_2CH_3), 1.06 (9H, s, Si^{t}Bu), 1.05 (9H, s, Si^{t}Bu), 1.00 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.94 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.50 (3H, d, *J* = 6.8 Hz, CHCH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 216.0, 132.6, 128.9, 86.5, 81.7, 78.0, 74.6, 50.2, 47.4, 44.2, 39.5, 38.8, 33.6, 28.5, 27.7, 27.3, 23.2, 21.6, 20.3, 15.6, 15.4, 14.5, 14.0, 12.5, 11.0, 10.6, 5.2; m/z (CI$^+$, NH_3) 541 (15, MH^+), 523 (25), 401(100), 383 (10), 343 (30), 315 (40), 285 (20), 257 (40), 215 (60); HRMS (CI, NH_3) Calcd for $C_{31}H_{61}O_5Si$ (M^++H) 541.4288. Found 541.4288.

The minor isomer **37** had R_f 0.25 (30% Et_2O/30-40 petrol); $[\alpha]_D^{20}$+13.6° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3490 (m br), 2965 (s), 2935 (s), 2860 (m), 1700 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (1H, t, *J* = 6.9 Hz, *H*C=C), 4.01-4.05 (1H, m, 2 x C*H*OSi), 3.79 (1H, s, C_3-O*H*), 3.75 (1H, br t, *J* = 6.7 Hz, C_3-*H*), 3.52 (1H, br d, *J* = 9.1 Hz, C_{11}-*H*), 3.31 (1H, br s, C_{11}-O*H*), 3.01 (1H, qd, *J* = 6.9, 4.1 Hz, C_{10}-*H* or C_8-*H*), 2.93 (1H, br q, *J* = 7.1 Hz, C_{10}-*H* or C_8-*H*), 2.59 (1H, br d, *J* = 12.8 Hz), 1.86-2.02 (3H, m), 1.52-1.73 (4H, m), 1.55 (3H, s, C=C(CH_3)), 1.33-1.42 (1H, m), 1.22 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.10 (3H, d, *J* = 7.2 Hz, CHCH_3), 1.03 (9H, s, Si^{t}Bu), 0.97 (9H, s, Si^{t}Bu), 0.93 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 0.92 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.90 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.75 (3H, d, *J* = 6.7 Hz, CHCH_3), 0.70 (3H, d, *J* = 6.6 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.9, 133.0, 128.6, 86.5, 81.5, 78.3, 74.6, 50.0, 46.5, 43.6, 39.5, 37.7, 33.3, 27.7 (2C), 27.1, 23.1, 21.2, 20.1, 15.8, 14.7, 14.4, 13.8, 12.7, 10.6, 8.7, 4.5. m/z (CI$^+$, NH_3) 541 (25, MH^+), 523 (35), 401(30), 383 (10), 343 (25), 315 (100), 285 (10), 257 (40), 215 (60); HRMS (CI, NH_3) Calcd for $C_{31}H_{61}O_5Si$ (M^++H) 541.4288. Found 541.4290.

The above procedure was employed using ketone **26** with racemic aldehyde **8**. The following quantities were used – ketone **26** (40 mg, 99.8 μmol), $TiCl_4$ (0.32 ml, 1.0 M CH_2Cl_2, 0.32 mmol), disopropylethylamine (40 μl, 0.23 mmol) in CH_2Cl_2 (3 ml). Flash chromatography gave **37** (36 mg, 67%) formed from (*S*)-**8** (previously the minor product) and its isomer **38** (15 mg, 30%) formed from (*R*)-**8**.

(3*R*,4*R*,5*S*,6*S*,7*S*,8*S*,10*R*,11*S*,12*R*)-3,11-Dihydroxy-4,6,8,10,12,14-hexamethyl-5,7-[[bis-(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-9-one (3-*epi*-38) and (3*R*,4*R*,5*S*,6*S*,7*S*,8*S*,10*R*,11*S*,12*S*)-3,11-Dihydroxy-4,6,8,10,12,14-hexamethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-9-one (3-*epi*-37). The same procedure as previously described for the synthesis of diols **37** and **38** was employed using the C_3-epimeric ketone **29** and (*R*)-**8** with the following quantities – ketone **29** (25 mg, 62.4 μmol), $TiCl_4$ (0.19 ml, 1.0 M CH_2Cl_2, 0.19 mmol), diisopropylethylamine (26 μl, 0.15 mmol) in CH_2Cl_2 (2 ml). Flash chromatography gave the major isomer 3-*epi*-**37** (21 mg, 60%) and the minor isomer 3-*epi*-**38** (7 mg, 20 %). The major isomer 3-*epi*-**37** had R_f 0.16 (30% Et_2O/30-40 petrol); $[\alpha]_D^{20}$+23.6° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3490 (w br), 2965 (s), 2930 (s), 2860 (m), 1690 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12 (1H, t, *J* = 6.9 Hz, *H*C=C), 4.20 (1H, dd, *J* = 9.7, 2.0 Hz, C*H*OSi), 4.04 (1H, dd, *J* = 9.8, 3.8 Hz, C*H*OSi), 3.57 (1H, dt, *J* = 7.5, 2.8 Hz, C_{11}-*H*), 3.45 (1H, dddd, *J* = 8.2, 8.0, 5.0, 5.0 Hz, C_3-*H*), 3.06 (1H, d, *J* = 8.2 Hz, C_3-O*H*), 3.04 (1H, d, *J* = 2.8 Hz, C_{11}-O*H*), 2.98 (1H, qd, *J* = 7.0, 3.8 Hz, C_{10}-*H* or C_8-*H*), 2.94 (1H, qd, *J* = 7.1, 3.0 Hz, C_{10}-*H* or C_8-*H*), 1.9-2.05 (4H, m, C_{13}-*H* & C_{16}-*H*), 1.63-1.75 (2H, m), 1.55-1.63 (2H, m), 1.54 (3H, s, C=C(CH_3)), 1.20-1.30 (1H, m), 1.23 (3H, d, *J* = 6.95 Hz, CHCH_3), 1.13 (3H, d, *J* = 7.2 Hz, CHCH_3), 1.02 (3H, d, *J* = 6.9 Hz, CHCH_3), 1.02 (9H, s, Si^{t}Bu), 0.98 (9H, s, Si^{t}Bu), 0.97 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.92 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.88 (3H, d, *J* = 6.4 Hz, CHCH_3), 0.73 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.4,

132.0, 128.8, 81.4, 80.2, 77.5, 74.5, 50.1, 46.7, 43.4, 39.1, 37.6, 33.2, 28.8, 27.7, 27.2, 23.0, 21.2, 20.1, 15.4, 15.2, 14.3, 13.8, 12.5, 10.7, 10.5, 9.9; m/z (CI$^+$, NH_3) 541 (5, MH$^+$), 523 (20), 401(100), 383 (10), 359 (100), 343 (10), 315 (40); HRMS (CI, NH_3) Calcd for $C_{31}H_{61}O_5Si$ (M+H$^+$) 541.4288. Found 541.4290.

The minor isomer 3-*epi*-**38** had R_f 0.21 (30% Et_2O/30-40 petrol); $[\alpha]_D^{20}$+12.0° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.12 (1H, t, *J* = 7.0 Hz, *H*C=C), 4.21 (1H, dd, *J* = 9.7, 2.0 Hz, C*H*OSi), 4.05 (1H, dd, *J* = 9.7, 4.0 Hz, C*H*OSi), 3.53 (1H, dt, *J* = 9.2, 1.8 Hz, C_{11}-*H*), 3.46 (1H, dddd, *J* = 8.2, 8.0, 5.0, 5.0 Hz, C_3-*H*), 3.33 (1H, d, *J* = 1.9 Hz, C_{11}-O*H*), 3.04 (1H, d, *J* = 8.2 Hz, C_3-O*H*), 3.02 (1H, qd, *J* = 6.9, 4.0 Hz, C_{10}-*H* or C_8-*H*), 2.94 (1H, qd, *J* = 7.1, 1.7 Hz, C_{10}-*H* or C_8-*H*), 2.61 (1H, br d, *J* = 12.9 Hz) 1.85-2.03 (3H, m, C_{13}-*H* & C_{16}-*H*), 1.55-1.75 (4H, m), 1.57 (3H, s, C=C(C*H*$_3$)), 1.20-1.30 (1H, m), 1.23 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.11 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.02 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.02 (9H, s, Si^{t}Bu), 0.98 (9H, s, Si^{t}Bu), 0.97 (3H, t, *J* = 7.5 Hz, CH_2C*H*$_3$), 0.92 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$), 0.74 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 0.7 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 218.0, 133.0, 128.6, 81.6, 80.2, 77.5, 74.6, 50.0, 46.5, 43.6, 39.4, 37.7, 33.3, 28.8, 27.7, 27.2, 23.0, 21.2, 20.1, 15.8, 14.7, 14.4, 13.9, 12.5, 10.7, 10.5, 8.7.

(4*R*,5*S*,6*S*,7*S*,8*S*,10*R*,12*R*)-4,6,8,10,12,14-Hexamethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-3,9,11-trione (35) and (4*R*,5*S*,6*S*,7*S*,8*S*,10*S*,12*R*)-4,6,8,10,12,14-Hexamethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-3,9,11-trione (34). Oxalyl chloride (0.46 ml, 2 M in CH_2Cl_2, 0.92 mmol) was dissolved in CH_2Cl_2 (5 ml) and cooled to –78 °C. A solution of DMSO (127 μl, 1.8 mmol) in CH_2Cl_2 (3 ml) was added *via* cannula and the mixture stirred for 5 min, followed by addition of the alcohol **38** (80 mg, 0.148 mmol) in CH_2Cl_2 (0.3 ml) *via* cannula. After 45 min, Et_3N (0.42 ml, 3.0 mmol) was added and stirring was continued at –78 °C for 15 min and then the reaction mixture was warmed to –5 °C (ice/salt) for 5 min. The reaction mixture was quenched by the addition of saturated NH_4Cl solution (20 ml), then allowed to warm to room temperature and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil containing some Et_3N•HCl. This residue was triturated with pentane (10 ml), filtered to remove the insoluble Et_3N•HCl, and concentrated *in vacuo* to give triketone **35** as an oil (80 mg, 100% crude). Attempted purification of this compound by silica gel chromatography resulted in epimerisation of the C_{10} stereocentre to give **34**. Similarly, exposure to Et_3N (2 equiv) in CH_2Cl_2 at room temperature for 45 min resulted in epimerisation at C_{10} to give a 1:1 mixture of the two epimers. The triketone **35** was therefore used without further purification for the subsequent cyclisation step to give denticulatin B (**2**). The C_{10} epimers could each be obtained in semi-pure form (<20% other epimer) by flash chromatography, thus purification of a sample of the crude triketone **35** (18 mg) gave **34** (9.4 mg, 52.2 %) and **35** (6.6 mg, 36.7 %).

35 had R_f 0.26 (2.5% Et_2O/CH_2Cl_2); IR ($CHCl_3$) 2970 (s), 2930 (s), 2860 (m), 1720 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.16 (1H, br t, *J* = 7.0 Hz, *H*C=C), 4.27 (1H, dd, *J* = 9.8, 2.7 Hz, C*H*OSi), 4.09 (1H, q, *J* = 7.1 Hz, C_{10}-H), 3.94 (1H, dd, *J* = 9.7, 3.0 Hz, C*H*OSi), 2.86-2.95 (1H, m), 2.84 (1H, qd, *J* = 7.1, 3.0 Hz), 2.58 (1H, qd, *J* = 7.0, 2.8 Hz), 2.46-2.56 (2H, m), 2.38 (1H, dd, *J* = 13.5, 5.6 Hz), 1.83-2.03 (4H, m), 1.57 (3H, s, C*H*$_3$C=), 1.29 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.25 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.11 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.03 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$), 0.97 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 0.97 (9H, s, Si^{t}Bu), 0.96 (9H, s, Si^{t}Bu), 0.92 (3H, t, *J* = 7.5 Hz, CH_2C*H*$_3$), 0.79 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1, 211.6, 208.6, 130.8, 129.9, 82.2, 80.6, 57.8, 49.8, 49.5, 43.2, 42.4, 38.8, 33.4, 27.7, 27.1, 23.1, 21.2, 20.0, 16.3, 15.6, 14.2, 14.0, 13.6, 12.5, 7.9, 7.7; m/z (CI$^+$, NH_3) 537 (100, MH$^+$), 519 (10), 479(10), 313 (20), 255 (30); HRMS (CI, NH_3) Calcd for $C_{31}H_{57}O_5Si$ (M+H$^+$) 537.3975. Found 537.3980.

34 had R_f 0.29 (2.5% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.12 (1H, br t, *J* = 7.0 Hz, *H*C=C), 4.29 (1H, dd, *J* = 9.7, 2.7 Hz, C*H*OSi), 4.07 (1H, dd, *J* = 9.5, 4.2 Hz, C*H*OSi), 3.97 (1H, q, *J* =

7.1 Hz, C_{10}-*H*), 2.81-2.95 (2H, m), 2.45-2.60 (3H, m), 2.27 (1H, dd, *J* = 13.0, 6.7 Hz), 1.83-2.01 (4H, m), 1.57 (3H, s, CH_3C=), 1.25 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.22 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 1.12 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.05 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 1.04 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 0.96 (18H, s, Si^tBu_2), 0.91 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 0.74 (3H, d, *J* = 6.8 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.9, 211.2, 207.6, 130.9, 129.8, 81.3, 80.3, 60.1, 51.3, 49.4, 43.3, 43.2, 39.5, 33.4, 27.6, 27.1, 23.0, 21.2, 20.0, 16.6, 15.7, 14.2, 13.4, 12.54, 12.5, 7.8, 7.7; m/z (CI^+, NH_3) 537 (100, MH^+), 519 (8), 479(10), 313 (25), 255 (25); HRMS (CI, NH_3) Calcd for $C_{31}H_{57}O_5Si$ ($M+H^+$) 537.3975. Found 537.3980.

This same procedure was applied to the oxidation of the alcohol 3-*epi*-**38** using the following quantities – 3-*epi*-**38** (18 mg, 36 μmol), oxalyl chloride (105 μl, 2.0 M CH_2Cl_2, 0.21 mmol), DMSO (29.5 μl, 0.41 mmol) and triethylamine (96 μl, 0.69 mmol). Purification by flash chromatography (2.5% Et_2O/CH_2Cl_2) gave a mixture of C_{10}-epimers, which were partially separated to give major isomer **35** (12.2 mg, 68.5%) and minor C_{10}-epimerised triketone **34** (3.1 mg, 17.2 %).

(–)-Denticulatin B (2). To a round bottom flask containing the triketone **35** (crude from the previous step) (0.08 g, 0.15 mmol) was added freshly prepared buffered pyridinium hydrofluoride (0.4 ml) (stock solution prepared from dry THF (5 ml), pyridine (2.5 ml), and pyridinium hydrofluoride (1.05 g)). The reaction mixture was stirred at room temperature for 4 h then diluted with CH_2Cl_2 (60 ml) and successively extracted with saturated aqueous $CuSO_4$ (4 x 20 ml), aqueous $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which slowly crystallised. Addition of pentane (3 ml) and trituration gave (–)-denticulatin B (**2**), which was collected by filtration using a Craig tube, as a crystalline solid (32 mg, 54%): mp 135-137 °C (pentane); R_f 0.25 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –29.3° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.38 (1H, br s, C_9-O*H*), 5.17 (1H, t, *J* = 7.0 Hz, *H*C=C), 4.38 (1H, dd, *J* = 10.7, 3.0 Hz, C_5-*H*), 3.54 (1H, dt, *J* = 8.5, 2.7 Hz, C_7-*H*), 3.27 (1H, d, *J* = 8.5Hz, C_7-O*H*), 2.91 (1H, q, *J* = 7.1 Hz, C_{10}-*H*), 2.68 (1H, dqd, *J* = 10.5, 6.8, 3.8 Hz, C_{12}-*H*), 2.51 (1H, qd, *J* = 6.8, 3.0 Hz, C_4-*H*), 2.50 (1H, dq, *J* = 17.8, 7.3 Hz, C_2-*H*), 2.41 (1H, dq, *J* = 17.8, 7.3 Hz, C_2-*H*), 2.26 (1H, dd, *J* = 13.8, 3.5 Hz, C_{13}-*H*), 1.98 (2H, dq, *J* = 7.5, 7.5 Hz, C_{16}-*H*), 1.70 (1H, dd, *J* = 13.8, 10.5 Hz, C_{13}-*H*), 1.55-1.70 (2H, m, C_6-*H* & C_8-*H*), 1.59 (3H, br s, C_{23}-CH_3), 1.17 (3H, d, *J* = 7.0 Hz, C_{20}-CH_3), 1.13 (3H, d, *J* = 7.0 Hz, C_{21}-CH_3), 1.03 (3H, t, *J* = 7.3 Hz, C_1-CH_3), 0.99 (3H, d, *J* = 6.8 Hz, C_{18}-CH_3), 0.94 (3H, d, *J* = 6.8 Hz, C_{19}-CH_3), 0.92 (3H, t, *J* = 7.5 Hz, C_{17}-CH_3), 0.89 (3H, d, *J* = 6.8 Hz, C_{22}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 219.5, 211.3, 131.3, 129.3, 101.9, 76.4, 69.1, 51.4, 46.8, 43.1, 42.1, 41.6, 37.5, 32.6, 21.2, 15.2, 14.7, 14.6, 14.2, 13.3, 12.6, 7.8, 7.4; ^{13}C NMR (C_6D_6, 100 MHz) δ 218.6, 209.3, 132.0, 129.5, 102.0, 76.3, 69.2, 52.1, 47.0, 43.1, 42.7, 41.7, 37.7, 32.4, 21.6, 15.4, 15.0, 14.8, 14.5, 13.3, 12.4, 8.1, 7.6; m/z (CI^+, NH_3) 379 (100, MH^+–H_2O), 361 (35), 311(15), 275 (50), 241 (30), 225 (60), 137 (80); HRMS (CI, NH_3) Calcd for $C_{23}H_{39}O_4$ (MH^+–H_2O) 379.2848. Found 379.2848.

(–)-Denticulatin A (1). The same procedure used for the deprotection of the crude triketone **35** was applied to a mixture of C_{10}-epimers, *i.e.* **34** and **35**, using the following quantities – triketones (22 mg, 41 μmol), HF/pyridine + pyridine (0.1 ml). Purification by flash chromatography gave (–)-denticulatin A (**1**) (4.3 mg, 26.7%) and (–)-denticulatin B (**2**) (8.3 mg, 51.5 %). Denticulatin B (**2**) had spectral characteristics identical to that already described and (–)-denticulatin A (**1**) had R_f 0.30 (10% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ –35.1° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.10 (1H, br s, C_9-O*H*), 5.12 (1H, t, *J* = 7.0 Hz, *H*C=C), 4.38 (1H, dd, *J* = 10.8, 2.9 Hz, C_5-*H*), 3.61 (1H, dt, *J* = 8.9, 2.7 Hz, C_7-*H*), 3.38 (1H, d, *J* = 8.9 Hz, C_7-O*H*), 2.93 (1H, dqd, *J* = 9.5, 6.8, 4.7 Hz, C_{12}-*H*), 2.74 (1H, q, *J* = 7.3 Hz, C_{10}-*H*), 2.53 (1H, dq, *J* = 17.9, 7.2 Hz, C_2-*H*), 2.52 (1H, m, C_4-*H*), 2.44 (1H, dq, *J* = 17.9, 7.2 Hz, C_2-*H*), 2.18 (1H, dd, *J* = 13.6, 4.2 Hz, C_{13}-*H*), 1.98 (2H, dq, *J* = 7.4, 7.4 Hz, C_{16}-*H*), 1.75-1.80 (1H, m, C_8-*H*), 1.72 (1H, dd, *J* = 13.6, 10.5 Hz, C_{13}-*H*), 1.59-1.70 (1H, m, C_6-*H*), 1.57 (3H, br s, C_{23}-CH_3), 1.19 (3H, d, *J* = 7.3 Hz, C_{21}-CH_3), 1.09 (3H, d, *J* = 7.1 Hz, C_{20}-CH_3), 1.03 (3H, d, *J* = 6.9 Hz, C_{18}-CH_3), 1.02 (3H, t, *J* = 7.2 Hz, C_1-CH_3), 0.95 (3H, d, *J* =

7.0 Hz, C_{19}-CH_3), 0.92 (3H, t, J = 7.2 Hz, C_{17}-CH_3), 0.91 (3H, d, J = 6.8 Hz, C_{22}-CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 219.0, 209.7, 131.7, 129.5, 103.0, 75.4, 69.7, 50.5, 47.2, 42.8, 42.5, 38.7, 37.7, 32.7, 21.6, 15.9, 15.6, 14.4, 13.5, 13.47, 11.9, 8.1, 7.9; m/z (CI^+, NH_3) 379 (100, MH^+-H_2O), 361 (40), 311(20), 275 (50), 241 (30), 225 (90), 137 (80); HRMS (CI, NH_3) Calcd for $C_{23}H_{39}O_4$ (MH^+-H_2O) 379.2848. Found 379.2848.

(4*R*,5*S*,6*S*,7*S*,8*S*,10*R*,12*S*)-4,6,8,10,12,14-Hexamethyl-5,7-[[bis(1,1-dimethylethyl)-silylene]dioxy]-heptadec-14-en-3,9,11-trione (39). The same procedure as previously described for the oxidation of the isomeric diol **38** was employed using the following quantities – diol **37** (30 mg, 55 μmol), oxalyl chloride (176 μl, 2.0 M CH_2Cl_2, 0.35 mmol), DMSO (49 μl, 0.69 mmol) and triethylamine (160 μl, 1.14 mmol). In this case, purification by flash chromatography (2.5% Et_2O/CH_2Cl_2) was accompanied by <10% epimerisation and gave triketone **39** (26 mg, 86 %) as an oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.11 (1H, br t, J = 7.0 Hz, HC=C), 4.25 (1H, dd, J = 9.8, 2.7 Hz, $CHOSi$), 4.05 (1H, q, J = 7.1 Hz, C_{10}-H), 3.96 (1H, dd, J = 9.6, 2.8 Hz, $CHOSi$), 2.80-2.92 (2H, m), 2.45-2.60 (3H, m), 2.27 (1H, dd, J = 13.5, 5.6 Hz), 1.80-2.00 (4H, m), 1.55 (3H, s, CH_3C=), 1.25 (6H, d, J = 7.1 Hz, 2 x $CHCH_3$), 1.11 (3H, d, J = 7.0 Hz, $CHCH_3$), 1.05 (3H, d, J = 6.8 Hz, $CHCH_3$), 1.02 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.96 (9H, s, Si^{t}Bu), 0.94 (9H, s, Si^{t}Bu), 0.89 (3H, t, J = 7.5 Hz, CH_2CH_3), 0.78 (3H, d, J = 6.7 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1, 211.4, 208.6, 130.8, 129.8, 82.1, 80.6, 58.0, 49.8, 49.5, 43.2, 43.1, 38.8, 33.4, 27.7, 27.1, 23.1, 21.2, 20.0, 16.7, 15.6, 14.1, 13.8, 13.2, 12.5, 7.9, 7.7.

This same procedure was applied to the oxidation of 3-*epi*-**37** using the following quantities – diol 3-*epi*-**37** (7 mg, 36 μmol), oxalyl chloride (66 μl, 2.0 M CH_2Cl_2, 0.13 mmol), DMSO (18.3 μl, 0.26 mmol) and triethylamine (61 μl, 0.44 mmol). In this case, purification by flash chromatography (2.5% Et_2O/CH_2Cl_2) gave a mixture of C_{10}-epimers (6.0 mg, 86%), which were partially separated to give mostly the triketone **39** along with its C_{10}-epimer. The major isomer had identical spectroscopic data to that obtained previously.

12-Epi-denticulatin A (10-*epi*-40) and 12-Epi-denticulatin B (40). The same procedure used for the deprotection of the triketone **35** was applied to **39** (having predominantly the C_{10} configuration corresponding to denticulatin B) using the following quantities – triketone **39** (16 mg, 32 μmol) and HF/pyridine + pyridine (0.1 ml). Purification by flash chromatography gave 12-*epi*-denticulatin A (10-*epi*-**40**) (1.4 mg, 11 %) and 12-epi-denticulatin B (**40**) (6 mg, 47.6 %). 12-Epi-denticulatin A (10-*epi*-**40**) had R_f 0.38 (10% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.45 (1H, br s, C_9-OH), 5.09 (1H, t, J = 7.0 Hz, HC=C), 4.41 (1H, dd, J = 10.8, 2.9 Hz, C_5-H), 3.59 (2H, m, C_7-H & C_7-OH), 2.95-3.05 (1H, m), 2.4-2.6 (4H, m), 2.20 (1H, dd, J = 13.8, 6.0 Hz, C_{13}-H) 1.96 (2H, dq, J = 7.4, 7.4 Hz, C_{16}-H), 1.70-1.80 (1H, m), 1.78 (1H, dd, J = 13.8, 7.9 Hz, C_{13}-H), 1.55-1.65 (2H, m, C_6-H), 1.57 (3H, br s, C_{23}-CH_3), 1.25 (3H, d, J = 7.4 Hz, CH_3), 1.07 (3H, d, J = 7.1 Hz, CH_3), 1.02 (3H, d, J = 6.8 Hz, CH_3), 1.01 (3H, t, J = 7.2 Hz, C_1-CH_3), 0.96 (3H, d, J = 6.8 Hz, CH_3), 0.91 (3H, t, J = 7.4 Hz, C_{17}-CH_3), 0.87 (3H, d, J = 6.7 Hz, CH_3); m/z (CI^+, NH_3) 379 (90, MH^+-H_2O), 361 (55), 311(10), 275 (80), 241 (45), 225 (40), 137 (100); HRMS (CI, NH_3) Calcd for $C_{23}H_{39}O_4$ (MH^+-H_2O) 379.2848. Found 379.2848.

12-*Epi*-denticulatin B (**40**) had R_f 0.31 (10% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.42 (1H, br s, C_9-OH), 5.13 (1H, t, J = 7.0 Hz, HC=C), 4.40 (1H, dd, J = 10.7, 2.9 Hz, C_5-H), 3.50 (1H, dt, J = 9.4, 2.5 Hz, C_7-H), 3.20 (1H, d, J = 9.4 Hz, C_7-OH), 2.92 (1H, q, J = 7.1 Hz, C_{10}-H), 2.40-2.65 (4H, m), 2.31 (1H, dd, J = 13.5, 5.3 Hz, C_{13}-H), 1.97 (2H, dq, J = 7.5, 7.5 Hz, C_{16}-H), 1.70 (1H, dd, J = 13.5, 9.0 Hz, C_{13}-H), 1.55-1.75 (2H, m, C_6-H & C_8-H), 1.57 (3H, br s, C_{23}-CH_3), 1.21 (3H, d, J = 7.0 Hz, CH_3), 1.11 (3H, d, J = 7.1 Hz, CH_3), 1.03 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.99 (3H, d, J = 6.8 Hz, CH_3), 0.95 (3H, d, J = 6.8 Hz, CH_3), 0.91 (3H, t, J = 7.3 Hz, CH_2CH_3), 0.90 (3H, d, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 219.5, 211.3, 131.1, 129.4, 102.6, (resonance obscured by chloroform), 69.2,

50.8, 46.9, 45.2, 41.9, 41.5, 37.6, 32.5, 21.2, 15.5, 15.1, 14.9, 14.2, 13.3 (2 x C), 7.8, 7.3; m/z (CI^+, NH_3) 379 (80, MH^+-H_2O), 361 (50), 311(15), 275 (60), 241 (20), 225 (60), 137 (100); HRMS (CI, NH_3) Calcd for $C_{23}H_{39}O_4$ (MH^+-H_2O) 379.2848. Found 379.2848.

Acknowledgement: We thank the SERC (GR/F73458) and Pfizer Central Research for support. We are grateful to Dr. Mary J. Garson (University of Queensland) for valuable discussions and for kindly providing comparison ^1H NMR spectra for the denticulatins.

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(*Received in UK* 16 *October* 1995; *accepted* 16 *November* 1995)