Laboratory emulation of polyketide biosynthesis: an iterative, aldol-based, synthetic entry to polyketide libraries using (*R*)- and (*S*)-1-(benzyloxy)-2-methylpentan-3-one, and conformational aspects of extended polypropionates

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Received (in Cambridge) 10th December 1998, Accepted 5th January 1999

Iterative, one-directional, boron-mediated aldol chain extensions, using the dipropionyl reagent (*R*)-1-(benzyloxy)-2-methylpentan-3-one **7**, have enabled the highly diastereoselective assembly of the stereoregular heptapropionates **5** and **6**. The synthetic sequence developed permits structural diversity through variation in the stereochemical nature of the aldolisation and reduction steps, together with the choice of the chiral ketone employed at each iteration. The heptapropionate **5** has been shown to represent an example of a fully flexible molecule, whose backbone nevertheless adopts a single preferred conformation. It forms part of a family of conformationally controlled polyols, exploiting the avoidance of *syn*-pentane interactions and the preference for preorganisation through intramolecular hydrogen bonding.

Introduction

In these modern times, the perceived diminishing returns from natural product screening are driving the development and application of combinatorial strategies to identify and optimise drug discovery leads. Consequently, there is a continuing interest in the construction of libraries based on the known classes of biopolymer.[1] The polyketides represent an important class of natural products associated with a broad spectrum of biological activity and whose structures encompass a rich array of molecular architecture.[2] Recently, the polyketides have come under scrutiny as a potential source of molecular diversity. The salient motifs of this biopolymer class, such as hydrocarbon backbones, polyoxygenation and multiple contiguous stereogenic centres, contrast with those of the more conventional peptidic and peptidomimetic libraries already available.[1] Indeed biosynthetic approaches to the generation of polyketide diversity, entailing the combinatorial reconstruction of existing biosynthetic pathways, are now well under way.[3] As a complementary approach, we envisaged the rational construction of libraries of novel, *unnatural* polyketides by exploiting aldol-based methodology previously developed within our laboratory. In this article, we present our synthetic studies highlighting the power of this approach to the iterative assembly of polyketide libraries. We also discuss the conformational preferences of some representative extended polypropionates having up to 12 contiguous stereogenic centres.

Results and discussion

Iterative assembly of extended polypropionates

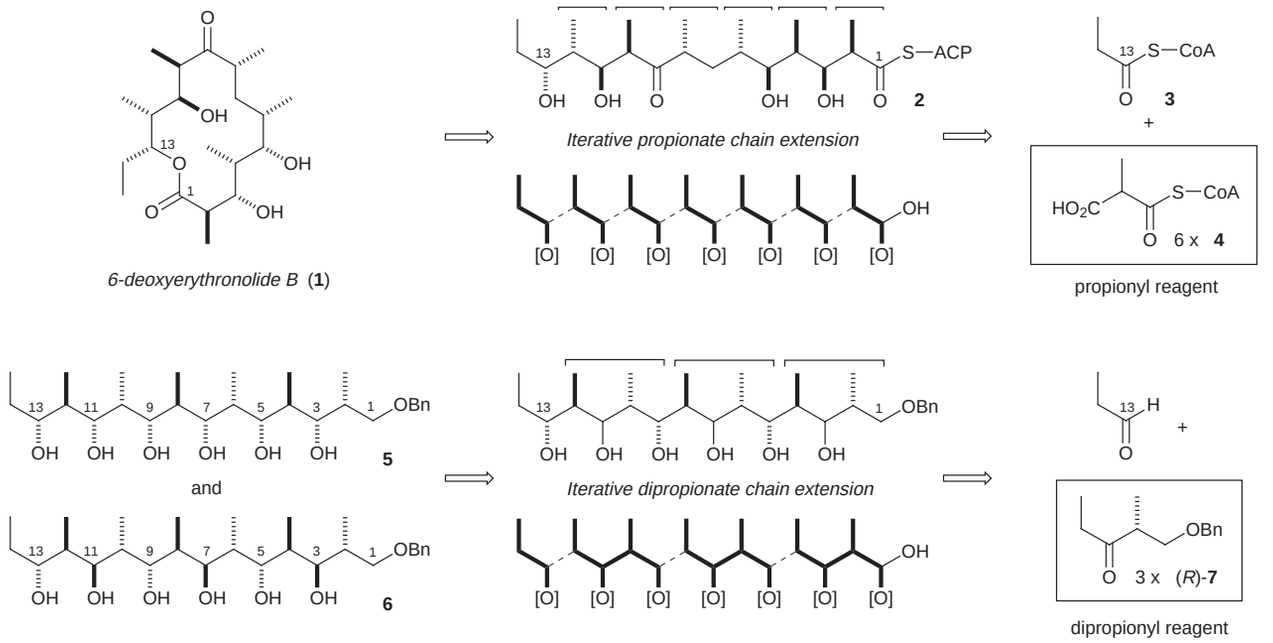
Our initial studies (Scheme 1) sought to emulate the processive mechanism of biosynthesis of bacterial polyketides, in which each chain extension unit introduced is correctly functionalised prior to addition of the next.[4] In the case of 6-deoxyerythronolide B (**1**), the primary heptapropionate framework in **2** is assembled by the appropriate polyketide synthase from a propionate starter unit **3** and 6 methyl malonyl extender units **4**.[5] We identified heptapropionates **5** and **6** as ideal targets by which to demonstrate biomimetic iterative chain extension utilising stereoselective aldol methodology.

Previously, we have introduced the ethyl ketone (*R*)-**7** and its enantiomer as versatile and powerful dipropionyl reagents for the synthesis of polypropionate-derived natural products and their value has been illustrated in a number of target-oriented synthetic ventures.[6,7] By appropriate choice of preformed enolate, three out of the four possible aldol diastereomers, *viz*. **8**,[7a] **9**[7b] and **10**,[7c] are readily accessible (Fig. 1) and this has enabled the development of a general protocol for the selective synthesis of all 32 stereoisomers of the stereopentad **11**.[7d] In this way, the synthesis of a large variety of natural and unnatural polypropionate subunits can be realised.

Using propionaldehyde as our starter unit, three iterative aldol chain extension cycles with (*R*)-**7** were planned to enable access to the hexols **5** and **6**. First, we required to establish protocols by which a common intermediate functionality could be efficiently regenerated. In previous studies, we had shown that selective generation of the (*E*)-enol dicyclohexylborinate of the ethyl ketones (*R*)- and (*S*)-**7** and aldol addition,[7a] followed by reduction[8] *in situ*, proceeds with excellent diastereoselection for the 1,3-*syn* diol. Using our standard enolisation procedure (Scheme 2),[6e,7a] *anti* aldol addition of (*R*)-**7** to propionaldehyde gave the intermediate aldolate **12**, which was reduced *in situ* with $LiBH_4$ to give the 1,3-*syn* diol **13** in 99% yield with 94% diastereoselection (ds).[9] Protection as its acetonide **14** (95%) enabled the stereochemistry of the aldol bond construction and reduction to be confirmed.† With the required stereotetrad so configured, the iterative protocol was completed by hydrogenolysis of the benzyl ether and Swern oxidation[10] to give the aldehyde **15** (93%), thereby regenerating the common aldehyde functionality. In this way, the tripropionate building block **15** was obtained in four steps from (*R*)-**7** in 88% yield with 94% ds.

With these optimum reaction conditions, we applied this *syn*-reduction iterative sequence twice successively. The boron-mediated aldol reaction of aldehyde **15** with the (*E*)-enolate of (*R*)-**7**, followed by *in situ* reduction with external hydride ($LiBH_4$), gave the 1,3-*syn* diol **16** in 78% yield with >97% ds. In this second iteration, the enhanced stereochemical fidelity is ascribed to a matched relationship of the coupling partners in the aldol bond construction.[11] Using the standard 3-step

† ^{13}C NMR resonances at 19.0, 30.2 and 98.3 ppm are characteristic of a *syn* acetonide and the large ^1H NMR vicinal coupling constants, $J_{3,4} = J_{4,5} = 10.4$ Hz are consistent with the preferred chair conformation. See reference 12.



Scheme 1 Iterative biosynthetic and synthetic polyketide construction.

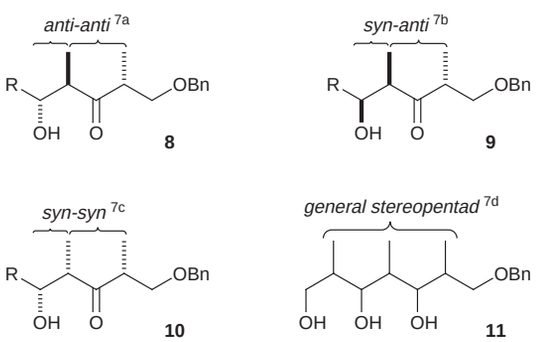


Fig. 1 Aldol diastereomers accessible from dipropionyl reagent (*R*)-**7**.

sequence (*cf*. **13**→**15**), this was elaborated into aldehyde **17** (88%) in readiness for a further chain extension. The third iteration again proceeded with matched induction to give the diol **18** (74%, >97% ds). Protection of **18** as its triacetonide **19** (97%) led to diagnostic ^{13}C NMR acetal resonances at 97.2, 97.1 and 96.8 ppm.[12] Overall, the protected 1,3-polyol **19** was obtained in 44% yield (10 steps) from the starting ketone (*R*)-**7**, with >88% ds for introduction of the 12 contiguous stereogenic centres. Finally, acetonide hydrolysis was effected with activated Dowex-50 resin to give the hexol **5** (89%) in which the hydroxys have an all-*syn* arrangement, combined with 1,3-*anti* methylation along the hydrocarbon backbone. The effective regeneration of a common intermediate functionality and high stereochemical and material efficiency of this sequence has led to its application on solid support, subject to appropriate modifications,[13] where the aldehyde starter unit is attached to a resin.

Introducing diversity by stereochemical and structural changes

Next we sought to demonstrate that library diversity could be introduced through stereochemical changes, in both the aldol bond construction and β-hydroxyketone reduction steps, as well as the introduction of substituents other than methyl into the backbone. First, the ketone reduction stereochemistry was reversed (Scheme 3). Using $Me_4NBH(OAc)_3$ for hydroxy-directed reduction[14] of **20** ‡ gave the 1,3-*anti* diol **21** (91%, >97% ds). Previously we had exploited the acetonide group as both protection for the 1,3-*syn* diol and as an endogenous stereochemical reporter in the ^{1}H and ^{13}C NMR spectra.[12] However, here we found it to be too labile under all hydrogenolysis conditions studied. Silylene protection of diol **21** alleviated this problem, with debenzylation then uneventfully providing the new tripropionate building block **22** (81%).

Following Swern oxidation, a second chain extension with (*R*)-**7** was performed to give the ketone **23** (72%, >97% ds). Application of the standard 3-step sequence (*cf*. **20**→**22**) then gave **24**, in readiness for a third dipropionate extension.§ As before, the *anti* aldol reaction of (*R*)-**7** with the aldehyde derived from **24** was followed by *anti* reduction, leading to diol **25** (60%). At this stage, silylene deprotection was carried out (HF·py) to give the hexol **6** (79%). In this sequence, the intermediate aldehydes were found to be prone to elimination if handled extensively and were, therefore, not isolated but subjected immediately to aldol chain extension.

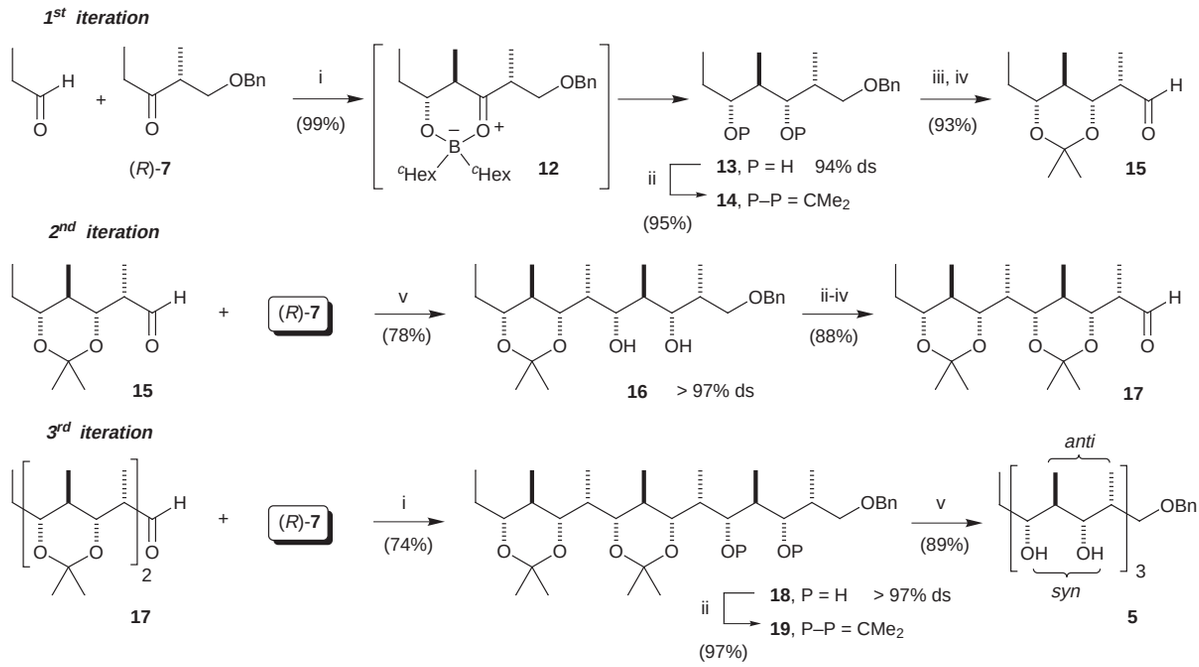
We now looked to introduce further diversity by variation of the ketone chain extension unit with regard to substitution and absolute configuration (Scheme 4). For example, an *anti* aldol reaction of the aldehyde **15** with the enantiomeric ketone (*S*)-**7** gave adduct **26** (79%) as the major isomer with 85% ds. In this more demanding mismatched case,[11] the high level of π-face selectivity from the (*E*)-enolate overrides any Felkin–Anh type influence from the aldehyde. Selecting (*R*)-**27**[8a] in the aldol reaction with **15** gave ketone **28** with high diastereoselectivity (>97% ds), as expected from the matched relationship of the coupling partners, demonstrating the potential for introducing substituents other than methyl in these extended polyketide systems. In previous work, we have demonstrated that alkoxy substituents (*e.g*. BnO, MeO) can also be employed without impairment of the reaction stereoselectivity.[16]

A family of conformationally controlled polyols

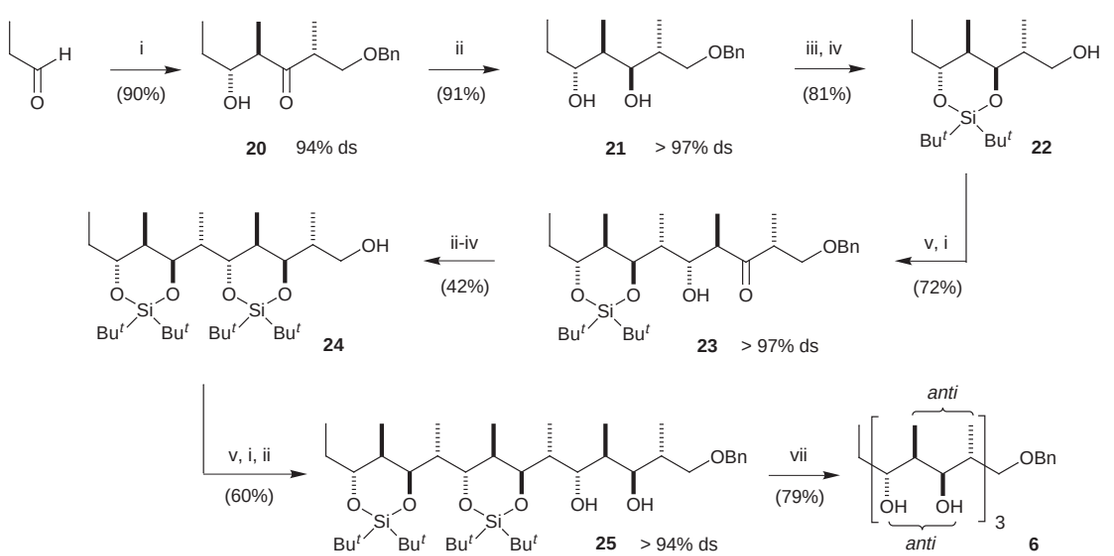
The heptapropionates **5** and **6** can be regarded as long chain *n*-alkanes upon which methyl and hydroxy substituents have been appended in a stereoregular manner. Both possess a 1,3-*anti* methylation pattern, the preferred conformation of which has been known from polymer chemistry for many years. Syndio-

‡ In all new aldol products, the *anti* relative configuration of the aldol bond was supported by the large vicinal coupling constant (J = 7.0–9.6 Hz) observed; the configuration of the new hydroxy-bearing centre was also established, in several cases, by ^{1}H NMR Mosher ester analysis. See reference 15.

§ The *anti* relative stereochemistry of the 1,3-diol was confirmed, at each iteration, by acetonide formation and ^{13}C NMR analysis. See reference 12.



Scheme 2 *Reagents and conditions*: (i) (*c*-Hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1.5 h; RCHO, −78→−15 °C, 3.5 h; LiBH$_4$, −78 °C, 2 h; H$_2$O$_2$, 10% NaOH, MeOH, 2 h; (ii) Me$_2$C(OMe)$_2$, PPTS, CH$_2$Cl$_2$, 5–18 h; (iii) Pd(OH)$_2$/C, H$_2$, EtOH, 1–4 h; (iv) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, 0.5 h; Et$_3$N, −78→−40 °C, 0.25 h; (v) Dowex-50, MeOH–H$_2$O (9 : 1), Δ, 4 h.



Scheme 3 *Reagents and conditions*: (i) (*R*)-**7**, (*c*-Hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1.5 h; RCHO, −78→−15 °C, 3.5 h; H$_2$O$_2$, pH 7 buffer, MeOH, 2 h; (ii) Me$_4$NBH(OAc)$_3$, AcOH–MeCN, −20 °C, 13–44 h; (iii) (*t*-Bu)$_2$Si(OTf)$_2$, 2,6-lutidine, CH$_2$Cl$_2$, 20 °C, 21–44 h; (iv) 10% Pd/C, H$_2$, EtOH, 1.5–3 h; (v) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, 0.5 h; Et$_3$N, −78→−40 °C, 0.25 h; (vi) HF·pyridine–pyridine, THF, 14 h, 20 °C.

tactic polypropylene, for example, exists in either extended chain[17a] or helical[17b] conformations in which destabilising *syn*-pentane interactions are avoided. With the additional presence of 1,3-related hydroxy groups in **5** and **6**, it was suspected that the polypropionate sequences generated might demonstrate pronounced conformational biases in solution. In general terms, it is of interest to identify structural units within molecules that can be exploited as 'conformational building blocks'.[18] Moreover, an understanding of the principles which render them conformationally restricted is important for the design of novel drugs and host molecules.[19]

Initially, we examined the monomeric *syn*-diol **13** (≡**29**, with $n = 1$, Fig. 2). The calculated global minimum conformer **30** (MM2, MacroModel, ver. 4.5)[20] shows that the 2-Me and 4-Me are oriented to avoid *syn*-pentane interactions whilst the hydroxy groups form an intramolecular hydrogen bonding network. To obtain experimental evidence for this population bias, we related the observed vicinal coupling constants to those predicted by MacroModel, using the Karplus-type routine[21] included in this package. For 3-H, the experimental ^3J values (1.4 and 9.5 Hz) compare favourably with those calculated (1.7 and 9.2 Hz) reflecting the *gauche* 2-H/3-H and *trans* 3-H/4-H relative orientations in **30**. The strong divergence of these two diagnostic coupling constants indicates a substantial population in solution of the calculated conformation.

Next, we examined the longer chain homologue **5** (≡**29**, $n = 3$, Fig. 3). Monte Carlo exploration of the accessible conformational space of hexol **5** gave **31** as the global minimum conformer. In an analogous manner to **13**, the alkane backbone adopts an extended all *trans* conformation (mean dihedral angle 168°) with an intramolecular hydrogen bonding network terminating on the benzyl ether oxygen. Vicinal ^{1}H NMR coupling constants again provided evidence for the solution phase conformation. For the methine protons of the hydroxy bearing

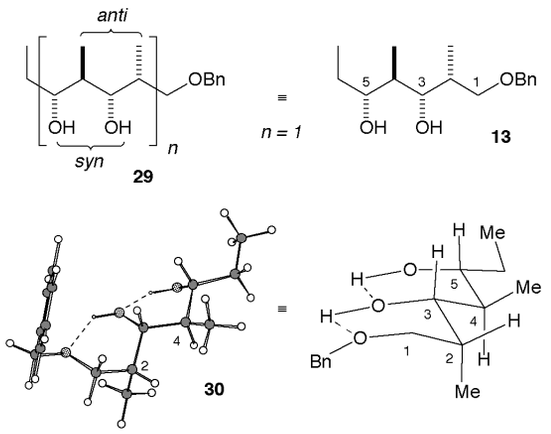


Fig. 2 Chem3D representation of the global minimum conformer **30** of diol **13**.

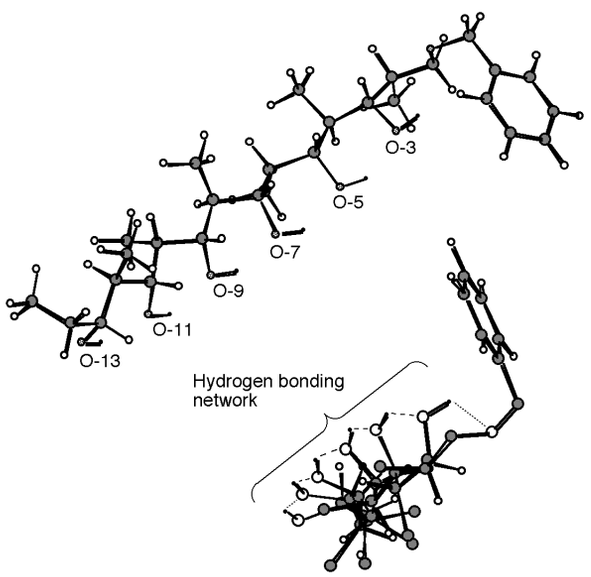
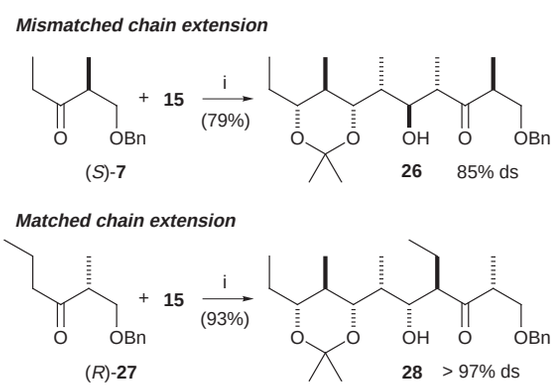


Fig. 3 Chem3D representations of the global minimum conformer **31** of hexol **5** (only selected H shown for clarity).



Scheme 4 *Reagents and conditions*: (i) (*c*-Hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1.5 h; **15**, −78→−15 °C, 3.5 h; H_2O_2, pH 7 buffer, MeOH, 2 h.

carbons in **5**, the calculated values fell into two distinct ranges, 0.6–1.7 Hz and 10.1–10.6 Hz, reflecting the dihedral angles associated with the *trans* conformations for the main chain. Although signal overlap prevented determination of all of the pertinent coupling constants, the observed ^3J values of 1.2, 1.3, 1.5, 1.7 and 9.1, 9.3, 9.4 Hz (500 MHz; C_6D_6) provide support for a strong bias in the conformer population in solution, toward that calculated *in vacuo*.

An extended intramolecular hydrogen bonding network, acting in concert with the constraint provided by the 1,3-*anti* methylation, was predicted by the preceding modelling results. By ^{1}H NMR spectroscopy, the hydroxy protons of **5** are markedly downfield in chemical shift (δ_H range 4.47–6.07 ppm in C_6D_6) and appear as six distinct singlets (Fig. 4). Over the concentration range of 0.5 mM to 77 mM, these chemical shifts have essentially constant values [$\Delta(\delta_H) \leq 0.08$ ppm, $CDCl_3$ (s)], supporting the existence of well-defined intramolecular hydrogen bonding networks (Fig. 5).

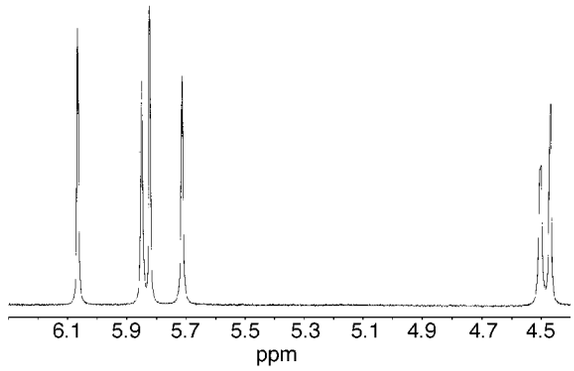


Fig. 4 Part of the ^{1}H NMR spectrum of hexol **5** (6.3 to 4.4 ppm, 300 K, C_6D_6 solution).

The molecular modelling also predicted that the methyl groups of the main chain (excluding the ethyl terminus) should split into two distinct chemical shift groupings, due to their distinct chemical environments in **31**. NOESY spectroscopy (500 MHz; C_6D_6) permitted assignment and the expected separation was observed: 1.15, 1.10, 1.04 ppm for the 1,5-*syn* methyl groups behind the plane (2-Me, 6-Me and 10-Me), whereas those in front (4-Me, 8-Me, 12-Me) appeared at 0.70, 0.60 and 0.55 ppm. Furthermore, these methyl groups exhibited quite distinct NOE patterns (Fig. 6) as expected from the preferred conformation **31**. This is most readily understood by considering the 6-Me and 8-Me groups. The modelling results predicted the 8-Me would show the observed NOE contacts with 7-H, 8-H, 9-H, and with 6-H and 10-H. Contrastingly, the 6-Me shows NOEs to 4-H, 6-H and 8-H but there are no observable NOEs to either 5-H or 7-H. In the global minimum conformer **31**, 5-H and 7-H adopt *trans* relationships (dihedral angles 165 and 177°) with respect to the 6-Me. Whilst absence of an NOE is a negative result, this is supportive of the local conformation in this subunit of the molecule. Moreover, neither the 2-Me (dihedral angle to 3-H, 164°) nor the 10-Me (dihedral angles to 9-H and 11-H, 165 and 177°) show NOE contacts to the methines of the adjacent hydroxy bearing carbons.

To complete the sequence, the shorter chain tetrol **32** (Scheme 5) was examined (≡**29**, $n = 2$). Acidic cleavage of the acetonide protecting group present in diol **16** afforded the tetrol **32** (76%). An entirely analogous pattern of behaviour was observed: well-defined downfield hydroxy chemical shifts (δ_H range 4.13–5.63 ppm in C_6D_6), correlation between the calculated[20,21] and observable ^3J values for the diagnostic methine protons (calculated ranges: 0.7–1.5 and 9.5–10.2 Hz; values observed: <1.0, 1.3, 1.8, 9.0, 9.4, 9.4 Hz) and distinctive chemical shift separation of the methyl groups in two different environments.

Seeking further evidence for the specific nature of the hydrogen bonding observed in hexol **5**, the diastereomeric hexol **6**, where the configurations at three of the six hydroxy bearing carbons (C_3, C_7 and C_{11}) had been inverted, was studied. In contrast to **5**, molecular modelling[20] of hexol **6** did not provide any distinct global minimum conformer. The calculated low energy conformers avoided unfavourable *syn*-pentane interactions, but no distinctive hydrogen bonding pattern emerged. Experimentally, the hydroxy groups of **6** are collapsed into a broad envelope in the ^{1}H NMR spectrum (500 MHz; $CDCl_3$),

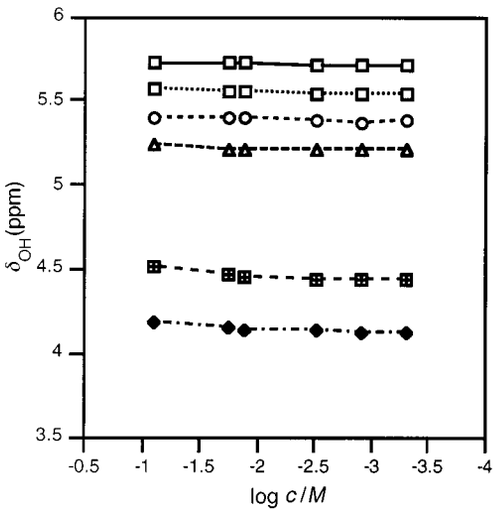


Fig. 5 ^{1}H NMR chemical shift (δ_{OH}) of the hydroxy protons at 300 K as a function of the logarithm of concentration for hexol **5** ($CDCl_3$ solution).

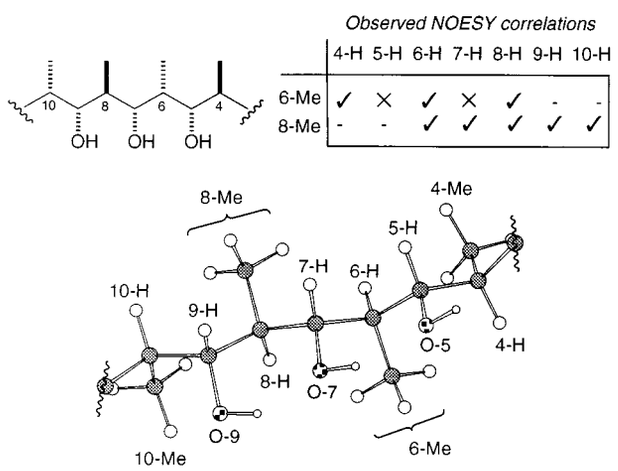
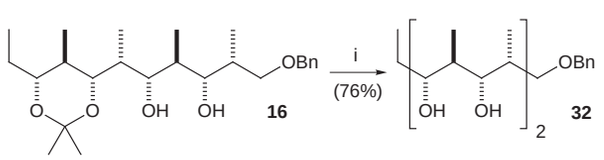


Fig. 6 Molecular fragment of hexol **5**, excised from the global minimum conformer **31**, with observed NOESY correlations (C_6D_6 solution).



Scheme 5 *Reagents and conditions*: (i) Dowex-50, MeOH–H_2O (9 : 1), Δ, 20 h.

preventing the observation of the vicinal coupling constants of the methines on the hydroxy bearing carbons. In this case, the 1,3-*anti* related hydroxy groups are presumably no longer all in an appropriate spatial arrangement to collectively hydrogen bond in solution. It can be concluded that the avoidance of *syn*-pentane interactions and intramolecular hydrogen bonding act in a synergistic manner in **5** leading to the population of essentially a single conformer in solution. These same two conformational determinants appear to be non-reinforcing in the diastereomeric hexol **6**. Notably, these two polyols have contrasting polarities (TLC) and solubility properties, *e.g.* **5** is readily soluble in benzene with R_f 0.37 (50% EtOAc–hexane) whilst in comparison, **6** is insoluble in this solvent exhibiting an R_f of 0.25 (10% MeOH–CH_2Cl_2). Diol **13**, tetrol **32** and hexol **5** can be considered to form part of a family of conformationally controlled polyols based on the structural subunit **33** (Fig. 7).

Achieving further structural diversity in polyketide libraries

These results demonstrate that the dipropionate reagents (*R*)- and (*S*)-**7** provide a practical method for the laboratory emulation of the iterative construction of extended polypropionate sequences.[22] However, the pressing question for polyketide libraries remains whether they can be made sufficiently diverse. Fortunately, further structural diversity is accessible by chain extending using other chiral enolate reagents developed within our laboratory. In a combinatorial context (Fig. 8), 5 different R substituents (*e.g.* Me,[7a] Et,[8a] Pr, OMe[16] and OBn[16]) together with the 2^4 accessible stereoisomers for each R, allows 80 possible sequences. As the chain length grows, the number of potential sequences rapidly escalates, with 6400 at the second iteration and 512000 at the third iteration. In principle, parallel synthesis (possibly on solid support[13]) should provide access to large libraries of stereochemically defined polyols, which might be further modified by appropriate functional group manipulation. Furthermore, such polyol structures are attractive in that they have directional hydrogen-bonding capability and provide quite subtle variability at a series of closely-spaced centres, complementary to the larger-scale repeat units present in peptidic and peptidomimetic sequences. Moreover, the readily attainable structural diversity, combined with the inherent conformational preferences of these flexible polyol structures, permits a high level of sampling of 3-dimensional space.

In closing, we note that modular polyketide synthases have remarkable scope[3] in their substrate specificity and this should allow for a variety of non-natural polyols to be elaborated by directed biosynthesis. In this way, a library of low molecular weight polyols, obtained by combinatorial synthesis, could potentially be translated to the higher levels of diversity typical of the clinically significant polyketide natural products. Such integration may prove beneficial in combinatorial approaches to even more diverse polyketide libraries.

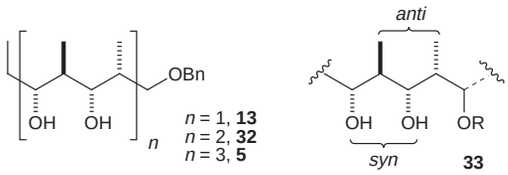


Fig. 7 A family of conformationally controlled propionates.

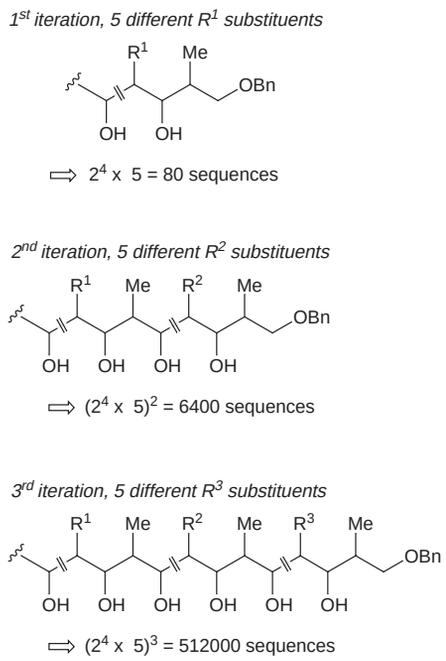


Fig. 8 Potential numbers of library components accessible at 1st, 2nd and 3rd iterations through stereochemical and substituent variation.

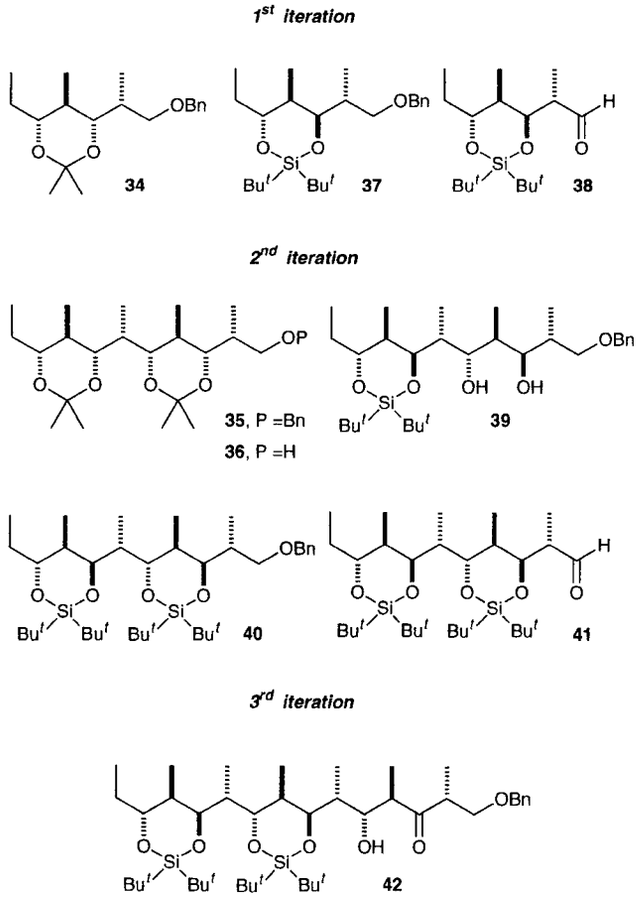


Fig. 9

Experimental

General

^{1}H NMR: 250, 400 or 500 MHz on Bruker DPX250, AM400, DRX400 or DRX500. ^{13}C NMR: 50.0, 62.9 or 100.6 MHz on Bruker AM200, DPX250, AM400 or DRX400. Spectra obtained in $CDCl_3$ were referenced to $CHCl_3$ ($\delta = 7.26$) for ^{1}H NMR and $CDCl_3$ ($\delta = 77.0$) for ^{13}C NMR. *J* values are given in Hz. NOESY correlations were determined with a mixing time of 1.5 s. The numbering of protons for assignment refers to the numbering of the carbon skeleton from the nascent terminus (see Scheme 1). $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and were measured at 20 °C on a Perkin Elmer 241 polarimeter. HPLC was carried out using a Rainan Instrument Co. Inc. DYNAMAX Macro-HPLC column with a flow rate of 10 cm^3 min^{-1}. GC analysis used a Hewlett Packard 5890 Series II GC with an HP5 capillary column. IR spectra were recorded on a Perkin Elmer 1620 FT-IR instrument. Melting points are uncorrected. Mass spectra were recorded by the EPSRC Mass Spectrometry Centre, Swansea. Microanalyses were carried out by the staff of the University Chemical Laboratory Microanalytical Department. Analytical TLC: precoated 0.25 mm Merck 60 F_{254} silica plates. Flash chromatography: Merck Kieselgel 60 (230–400 mesh). All experiments were carried out under an argon atmosphere with anhydrous solvents unless otherwise stated. Solvents and reagents were purified and dried according to standard procedures. Diastereoselectivities were determined by a combination of ^{1}H NMR, GC (following silylation with TMS imidazole–pyridine) and/or HPLC analysis.

Molecular modelling

Molecular modelling studies were performed on a Silicon Graphics Iris and Indigo cluster using the MacroModel program (ver. 4.5) developed by Still and co-workers.[20] Structures were subjected to a minimisation procedure into the nearest local minimum prior to the generation of new low energy conformers by Monte Carlo searching. A 20 kJ mol^{-1} cut off was employed, with experiments generally sampling batches of 2000 structures. Calculations were performed *in vacuo*.

General procedure A. The isolated aldolate was taken up in MeOH and pH 7 buffer (1 : 1, 10 cm^3 per mmol of aldolate) and stirred at 0 °C. Hydrogen peroxide (30% aqueous; 1.0 cm^3 per mmol of boron) was added dropwise and the mixture stirred at RT for 1–2 h. Dilution with H_2O, extraction with CH_2Cl_2, drying of the combined organics ($MgSO_4$) and evaporation *in vacuo* gave the crude aldol products which were, in general, purified by flash chromatography. For large scale preparations, a reductive wash of the combined organics ($NaSO_3$) was generally employed.

General procedure B. The isolated boronate was taken up in MeOH and 10% NaOH (2 : 1, 4 cm^3 per mmol of boronate) and stirred at 0 °C. Hydrogen peroxide (30% aqueous; 1.1 cm^3 per mmol of boron) was added dropwise and the mixture stirred at RT for 1–2 h. Dilution with H_2O, extraction with CH_2Cl_2, drying of the combined organics ($MgSO_4$) and evaporation *in vacuo* gave the crude diol products which were, in general, purified by flash chromatography.

(*R*)- and (*S*)-1-Benzyloxy-2-methylpentan-3-one 7

These were prepared according to our previously reported three-step procedure from (*R*)- and (*S*)-methyl 3-hydroxy-2-methylpropionate, respectively.[6e]

(*R*)-1-Benzyloxy-2-methylhexan-3-one 27

This was prepared by a modification of our existing 3-step procedure for the synthesis of (*R*)-**7**.[6e] Substitution of PrMgCl in place of EtMgBr in the third step gave (*R*)-**27** as a colourless oil; $[a]_D^{20}$ −19.9 (*c* 2.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 1730s (C=O), 1604m; δ_H (500 MHz; $CDCl_3$) 7.35–7.22 (5H, m, Ar*H*), 4.50 and 4.47 (2H, AB_q, *J* 12.0, CH_2Ph), 3.64 (1H, dd, *J* 9.0, 7.9, 1-H$_A$), 3.46 (1H, dd, *J* 9.0, 5.5, 1-H$_B$), 2.91–2.83 (1H, m, 2-H), 2.47 (1H, t, *J* 7.3, 4-H$_A$), 2.46 (1H, t, *J* 7.3, 4-H$_B$), 1.64–1.56 (2H, ddq, *J* 7.3, 7.3, 7.3, 5-H), 1.07 (3H, d, *J* 7.1, 2-Me), 0.90 (3H, t, *J* 7.4, CH_2CH_3); δ_C (50.3 MHz; $CDCl_3$) 213.1, 138.1, 128.3, 128.0, 127.5, 73.2, 72.3, 46.3, 44.0, 16.6, 13.7, 13.5; *m/z* (FAB) 221 (MH$^+$, 93%), 219 (100), 181 (26), 143 (12), 137 (12), 123 (42), 113 (55), 107 (22), 105 (15); HRMS (FAB) Calc. for $C_{14}H_{21}O_2$ (MH$^+$) 221.1541. Found 221.1536.

(2*R*,4*R*,5*R*)-1-(Benzyloxy)-5-hydroxy-2,4-dimethylheptan-3-one 20

To a stirred solution of (*c*-Hex)$_2$BCl (0.31 cm^3, 1.45 mmol) in Et_2O (4 cm^3) was added Et_3N (0.22 cm^3, 1.55 mmol) and the mixture was cooled to −15 °C. The ketone (*R*)-**7** (0.20 g, 0.97 mmol) in Et_2O (1.5 cm^3) was added *via* cannula and the reaction mixture stirred for 2 h at −15 °C. A solution of EtCHO (0.10 cm^3, 1.45 mmol) in Et_2O (5 cm^3) was added *via* cannula and stirring continued for 2 h. The reaction mixture was then partitioned between Et_2O (3 × 15 cm^3) and pH 7 buffer (10 cm^3). The organic extracts were concentrated *in vacuo* to give an oil which was oxidised according to procedure A. Flash chromatography (10% Et_2O–CH_2Cl_2) gave the aldol product **20** (0.23 g, 90%) as a colourless oil (Found C 72.7, H 9.2. Calc. for $C_{16}H_{24}O_3$: C 72.7, H 9.15%); $[a]_D^{20}$ −0.3 (*c* 2.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3463br (OH), 2971s, 2935s, 2877s, 1710s (C=O); δ_H (500 MHz; $CDCl_3$) 7.37–7.24 (5H, m, Ar*H*), 4.46 and 4.50 (2H, AB_q, *J* 10.6, CH_2Ph), 3.69 (1H, dd, *J* 8.8, 8.8, 1-H$_A$), 3.67–3.58 (1H, m, 5-H), 3.44 (1H, dd, *J* 8.8, 4.9, 1-H$_B$), 3.13–3.03 (1H, m, 2-H), 2.78 (1H, d, *J* 6.3, O*H*), 2.73 (1H, dq, *J* 7.0, 7.0,

4-H), 1.62–1.54 (1H, m, 6-H_A), 1.44–1.34 (1H, m, 6-H_B), 1.13 (3H, d, *J* 7.2, CHCH_3), 1.05 (3H, d, *J* 7.0, CHCH_3), 0.96 (3H, t, *J* 7.4, 6-Me); δ_C (100 MHz; $CDCl_3$) 218.0, 137.7, 128.3, 127.6, 127.6, 74.8, 73.3, 72.2, 51.5, 45.3, 27.3, 13.7, 13.5, 9.9; *m*/*z* (CI) 282 (M + NH_4^+, 16%), 265 (MH^+, 4), 247 ($MH^+ - H_2O$, 3), 224 (100), 207 (65), 108 (16); HRMS (CI) Calc. for $C_{16}H_{25}O_3$ (MH^+) 265.1804. Found 265.1799.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyloxy-2,4-dimethylheptane-3,5-diol 13

To a stirred solution of (*c*-Hex)$_2$BCl (4.9 cm^3, 22.5 mmol) in Et_2O (30 cm^3) was added Et_3N (3.4 cm^3, 24.0 mmol) and the mixture was cooled to −78 °C. A solution of the ketone (*R*)-**7** (3.09 g, 15.0 mmol) in Et_2O (16.5 cm^3) was added *via* cannula and the mixture stirred 30 min at −78 °C then at 0 °C for 1.5 h. After recooling to −78 °C, a solution of EtCHO (1.45 g, 26.3 mmol) in Et_2O (10.5 cm^3) was added *via* cannula and stirring continued at −78 °C for 30 min before warming to −15 °C for 3.5 h. The resultant solution was then recooled to −78 °C and precooled (−78 °C) before $LiBH_4$ (37.5 cm^3 of a 2 M THF solution, 75.0 mmol) was added. After 2 h, the reaction mixture was partitioned between Et_2O (3 × 150 cm^3) and NH_4Cl solution (200 cm^3), the organic extracts combined, concentrated *in vacuo* and the residue oxidised according to procedure B. Flash chromatography (25% EtOAc–hexane) and high vacuum drying (8 h/0.4 mmHg) gave the diol **13** (3.98 g, 99%) as a colourless oil. 400 MHz ^{1}H NMR analysis of the crude indicated ⩾94% ds. The major isomer was isolated diastereomerically pure by HPLC; R_t 24.0 min (40% EtOAc–hexane); $[\alpha]_D^{20}$ +5.6 (*c* 1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3374br (OH), 2966vs, 2931s, 2876s; δ_H (500 MHz; $CDCl_3$) 7.38–7.27 (5H, m, Ar*H*), 4.54 and 4.52 (2H, AB_q, *J* 12.0, CH_2Ph), 3.97 (1H, s br, O*H*), 3.81 (1H, dd, *J* 9.5, 1.4, 3-H), 3.74 (1H, s br, O*H*), 3.64–3.55 (3H, m, 5-H, 1-H_A, 1-H_B), 1.97–1.90 (1H, m, 2-H), 1.70–1.60 (2H, m, 4-H, 6-H_A), 1.46–1.37 (1H, m, 6-H_B), 0.99 (3H, d, *J* 6.7, CHCH_3), 0.97 (3H, t, *J* 7.3, 6-Me), 0.74 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 137.6, 128.5, 127.8, 127.6, 79.6, 77.3, 75.6, 73.5, 40.2, 35.0, 27.1, 12.6, 9.3, 9.1; *m*/*z* (CI) 267 (MH^+, 100%), 249 ($MH^+ - H_2O$, 3); HRMS (CI) Calc. for $C_{16}H_{27}O_3$ (MH^+) 267.1960. Found 267.1960.

(2*R*,3*S*,4*R*,5*R*)-1-Benzyloxy-3,5-isopropylidenedioxy-2,4-dimethylheptane 14

To a stirred solution of diol **13** (3.48 g, 13.1 mmol) in CH_2Cl_2 (20 cm^3) was added 2,2-dimethoxypropane (40.1 cm^3), followed by PPTS (5 crystals) and stirring was continued for 8 h. Solid $NaHCO_3$ (30 mg) was then added, the solvent removed *in vacuo*, and the residue purified by flash chromatography (5% Et_2O–hexane) to give the acetonide **14** as a colourless oil (3.84 g, 95%); $[\alpha]_D^{20}$ −15.8 (*c* 2.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2966s, 2935s, 2852s, 1453m; δ_H (500 MHz; $CDCl_3$) 7.36–7.26 (5H, m, Ar*H*), 4.53 and 4.49 (2H, AB_q, *J* 12.0, CH_2Ph), 3.68 (1H, dd, *J* 10.4, 2.0, 3-H), 3.48 (1H, dd, *J* 8.8, 8.6, 1-H_A), 3.37 (1H, ddd, *J* 10.4, 8.2, 2.6, 5-H), 3.31 (1H, dd, *J* 8.8, 6.3, 1-H_B), 2.10–2.03 (1H, m, 2-H), 1.68 (1H, m, 6-H_A), 1.46 (1H, ddq, *J* 10.4, 10.4, 6.9, 4-H), 1.38 (3H, s, C(CH_3)CH$_3$), 1.41–1.34 (1H, m, 6-H_B (Part. obs.)), 1.33 (3H, s, C(CH$_3$)CH_3), 0.92 (3H, t, *J* 7.4, 6-Me), 0.86 (3H, d, *J* 6.9, CHCH_3), 0.74 (3H, d, *J* 6.6, CHCH_3); δ_C (100 MHz; $CDCl_3$) 138.8, 128.3, 127.5, 127.4, 97.6, 75.5, 73.3, 73.1, 73.0, 34.6, 34.0, 30.1, 25.9, 19.7, 11.6, 9.5, 9.4; *m*/*z* (CI) 307 (MH^+, 82%), 291 (18), 266 (20), 249 (100), 141 (12), 108 (18), 99 (25), 91 (15); HRMS (CI) Calc. for $C_{19}H_{31}O_3$ (MH^+) 307.2273. Found 307.2273.

(2*R*,3*S*,4*R*,5*R*)-3,5-Isopropylidenedioxy-2,4-dimethylheptan-1-ol 34

To a stirred solution of the benzyl ether **14** (1.48 g, 4.8 mmol) in EtOH (21 cm^3) was added 20% $Pd(OH)_2$/C (0.2 g) and the mixture stirred under a hydrogen atmosphere for 4.25 h at RT. The catalyst was removed by filtration through Celite and the solvent concentrated *in vacuo* to give a colourless oil. Purification by flash chromatography (15% EtOAc–hexane) yielded the product **34** (see Fig. 9) (1.04 g, 95%) and allowed separation of the minor diastereomer (⩽6% by weight); $[\alpha]_D^{20}$ −6.9 (*c* 1.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3407br (OH), 2967vs, 2937vs, 2878s; δ_H (500 MHz; $CDCl_3$) 3.74 (1H, dd, *J* 10.2, 2.4, 3-H), 3.78–3.71 (1H, m, 1-H_A), 3.68–3.59 (1H, m, 1-H_B), 3.46 (1H, ddd, *J* 10.2, 8.6, 2.6, 5-H), 2.44 (1H, d, *J* 7.9, O*H*), 1.92–1.84 (1H, m, 2-H), 1.73–1.64 (1H, m, 6-H_A), 1.50 (1H, ddq, *J* 10.2, 10.2, 6.6, 4-H), 1.44 (3H, s, C(CH_3)CH$_3$), 1.42–1.32 (1H, m, 6-H_B (Part. obs.)), 1.36 (3H, s, C(CH$_3$)CH_3), 0.98 (3H, d, *J* 7.1, CHCH_3), 0.92 (3H, t, *J* 7.4, 6-Me), 0.74 (3H, d, *J* 6.6, CHCH_3); δ_C (50 MHz; $CDCl_3$) 97.6, 77.4, 75.4, 67.9, 34.8, 34.8, 30.1, 25.8, 19.8, 11.6, 9.4, 9.0; *m*/*z* (CI) 217 (MH^+, 62%), 201 (12), 176 (40), 159 (100), 139 (27), 108 (46); HRMS (CI) Calc. for $C_{12}H_{25}O_3$ (MH^+) 217.1803. Found 217.1804.

(2*S*,3*R*,4*R*,5*R*)-3,5-Isopropylidenedioxy-2,4-dimethylheptanal 15

To a stirred solution of oxalyl chloride (0.67 cm^3, 7.7 mmol) in CH_2Cl_2 (28 cm^3) at −78 °C was added *via* cannula a solution of DMSO (0.96 cm^3, 13.5 mmol) in CH_2Cl_2 (6.2 cm^3) and the mixture stirred for 5 min. The alcohol **34** (0.43 g, 2.0 mmol) was added *via* cannula in CH_2Cl_2 (6 cm^3) and the resultant solution stirred at −78 °C for 45 min. Et_3N (3.6 cm^3, 25.8 mmol) was added and stirring continued at −78 °C for 15 min and at −41 °C for 15 min. The reaction was partitioned between NH_4Cl solution (30 cm^3) and CH_2Cl_2 (3 × 60 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant yellow oil was triturated with cold hexane (3 × 10 cm^3), filtered through Celite and concentrated *in vacuo* to give the product **15** as a pale yellow oil (0.41 g, 98%). The product was stable to flash chromatography but in practice could be shown to be pure by ^{1}H NMR and was used directly; $[\alpha]_D^{20}$ +30.4 (*c* 1.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 2984s, 2940s, 2851m, 2716w (C*H*O), 1732s (C=O), 1456m; δ_H (400 MHz; $CDCl_3$) 9.63 (1H, s, C*H*O), 4.09 (1H, dd, *J* 10.4, 2.5, 3-H), 3.45 (1H, ddd, *J* 10.4, 8.2, 2.6, 5-H), 2.47 (1H, dq, *J* 7.0, 2.5, 2-H), 1.68 (1H, ddq, *J* 10.4, 7.4, 2.6, 6-H_A), 1.53–1.44 (1H, m, 4-H), 1.40 (3H, s, C(CH_3)CH$_3$), 1.42–1.32 (1H, m, 6-H_B (Part. obs.)), 1.30 (3H, s, C(CH$_3$)CH_3), 1.10 (3H, d, *J* 7.0, CHCH_3), 0.92 (3H, t, *J* 7.4, 6-Me), 0.78 (3H, d, *J* 6.7, CHCH_3); δ_C (100 MHz; $CDCl_3$) 204.8, 98.0, 75.2, 73.4, 47.2, 34.4, 29.8, 25.8, 19.5, 11.6, 9.3, 6.2.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*)-1-Benzyloxy-7,9-isopropylidenedioxy-2,4,6,8-tetramethylundecane-3,5-diol 16

To a stirred solution of (*c*-Hex)$_2$BCl (0.43 g, 2.0 mmol) and Et_3N (0.20 g, 2.0 mmol) in Et_2O (11 cm^3) at −78 °C was added, *via* cannula, a solution of ketone (*R*)-**7** (0.31 g, 1.5 mmol) in Et_2O (6 cm^3). The resultant solution was stirred for 0.5 h at −78 °C and 1 h at 0 °C. After recooling to −78 °C, a solution of aldehyde **15** (0.21 g, 1.0 mmol) in Et_2O (2.1 cm^3) was added *via* cannula and stirring continued at this temperature for 0.5 h and at 0 °C for 1 h. Recooling to −78 °C was followed by addition of a precooled (−78 °C) solution of $LiBH_4$ (2.5 cm^3 of a 2 M THF solution, 5.0 mmol). After 2 h at this temperature, the solution was partitioned between NH_4Cl solution (100 cm^3) and Et_2O (3 × 100 cm^3). The combined organics were concentrated *in vacuo* and oxidised according to procedure B. Flash chromatography (10% EtOAc–hexane) and HPLC (10% EtOAc–hexane) yielded the diol **16** (0.33 g, 78%) as colourless crystals (Found C 71.1, H 10.0. Calc. for $C_{25}H_{42}O_5$: C 71.0, H 10.0; mp 59–60 °C (pentane); $[\alpha]_D^{20}$ −3.0 (*c* 3.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3444br (OH), 2971vs, 2937s, 2855s; δ_H (500 MHz; $CDCl_3$) 7.33–7.24 (5H, m, Ar*H*), 4.84 (1H, s, O*H*), 4.52 and 4.57 (2H, AB_q, *J* 12.0, CH_2Ph), 4.25 (1H, s, O*H*), 3.78–3.71 (3H, m, OC*H*), 3.62 (1H, dd, *J* 8.9, 6.8, OC*H*), 3.42–3.38 (2H, m, OC*H*), 2.03–1.92 (2H, m, 6-H, 4-H), 1.78–1.63 (2H, m,

10-H_A, 8-H), 1.47 (3H, s, C(CH_3)CH_3), 1.43–1.35 (1H, m, 10-H_B (Obscured)), 1.37 (3H, s, C(CH_3)CH_3), 0.93 (3H, d, *J* 7.4, CHCH_3), 0.92 (3H, t, *J* 7.4, 10-Me), 0.91 (3H, d, *J* 7.4, CHCH_3), 0.74 (3H, d, *J* 6.6, CHCH_3), 0.72 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 138.9, 128.2, 127.6, 127.3, 98.1, 83.5, 81.1, 76.0, 75.3, 74.3, 73.2, 38.1, 35.9, 34.7, 34.0, 30.0, 25.7, 19.8, 13.1, 11.6, 9.4, 9.3, 4.7; *m*/*z* (CI) 423 (MH^+, 100%), 366 (8), 365 (35), 347 (15); HRMS (CI) Calc. for $C_{25}H_{43}O_5$ (MH^+) 423.3110. Found 423.3110.

(2*R*,3*S*,4*S*,5*S*,6*S*,7*R*,8*R*,9*R*)-1-Benzyloxy-3,5:7,9-bis(isopropylidenedioxy)-2,4,6,8-tetramethylundecane 35

Diol **16** (86.4 mg, 0.20 mmol) was stirred in dimethoxypropane (1.25 cm^3, 10.2 mmol) and CH_2Cl_2 (0.5 cm^3). PPTS (3 mg) was added and the mixture stirred for 18 h. Concentration *in vacuo* and flash chromatography (5% EtOAc–hexane) gave the diacetonide **35** (88.7 mg, 94%) as a colourless oil; $[a]_D^{20}$ −10.7 (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 2965s, 2936s, 2877s, 1728w; δ_H (500 MHz; $CDCl_3$) 7.34–7.26 (5H, m, Ar*H*), 4.49 and 4.51 (2H, AB_q, *J* 12.0, CH_2Ph), 3.66 (1H, dd, *J* 10.4, 2.1, 3-H), 3.57 (1H, dd, *J* 9.9, 1.9, 5-H), 3.55 (1H, dd, *J* 10.1, 1.7, 7-H), 3.48 (1H, dd, *J* 8.9, 8.2, 1-H_A), 3.37 (1H, ddd, *J* 10.1, 7.9, 2.7, 9-H), 3.31 (1H, dd, *J* 8.9, 6.4, 1-H_B), 2.14–2.06 (1H, m, 2-H), 1.93–1.86 (1H, m, 6-H), 1.62–1.74 (2H, m, 4-H, 10-H_A), 1.47 (1H, ddq, *J* 10.1, 10.1, 6.6, 8-H), 1.41 (3H, s, C(CH_3)CH_3), 1.43–1.34 (1H, m, 10-H_B (Obscured)), 1.37 (3H, s, C(CH_3)CH_3), 1.34 (3H, s, C(CH_3)CH_3), 1.27 (3H, s, C(CH_3)CH_3), 0.98 (3H, d, *J* 7.5, 6-Me), 0.92 (3H, t, *J* 7.4, 10-Me), 0.84 (3H, d, *J* 6.9, 2-Me), 0.77 (3H, d, *J* 6.6, 8-Me), 0.75 (3H, d, *J* 6.8, 4-Me); δ_C (100 MHz; $CDCl_3$) 138.8, 128.3, 127.5, 127.4, 97.2, 97.1, 76.3, 75.6, 73.4, 73.2, 73.1, 38.2, 35.9, 35.3, 33.9, 32.5, 30.2, 30.0, 25.9, 19.7, 19.7, 12.5, 11.9, 10.7, 9.6, 9.4; *m*/*z* (CI) 463 (MH^+, 65%), 405 (61), 347 (100), 329 (90), 239 (34), 157 (61), 139 (28); HRMS (CI) Calc. for $C_{28}H_{47}O_5$ (MH^+) 463.3423. Found 463.3423.

(2*R*,3*S*,4*S*,5*S*,6*S*,7*R*,8*R*,9*R*)-3,5:7,9-Bis(isopropylidenedioxy)-2,4,6,8-tetramethylundecan-1-ol 36

To a stirred solution of the diacetonide **35** (31.2 mg, 0.067 mmol) in EtOH (1.0 cm^3) was added 20% $Pd(OH)_2$/C (5 mg) and the mixture stirred under a hydrogen atmosphere for 1 h. The catalyst was removed by filtration through Celite and the solvent concentrated *in vacuo*. Purification by flash chromatography (25% Et_2O–hexanes) yielded the product **36** (24.2 mg, 96%) as a colourless oil; $[a]_D^{20}$ −6.0 (*c* 2.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3408br (OH), 2966s, 2878s; δ_H (500 MHz; $CDCl_3$) 3.73 (2H, dd, *J* 10.4, 2.4, 1-H_A, 3-H), 3.65–3.59 (1H, m, 1-H_B), 3.57 (2H, dd, *J* 10.1, 1.9, 5-H, 7-H), 3.36 (1H, ddd, *J* 10.1, 7.6, 2.3, 9-H), 2.54 (1H, br s, O*H*), 1.93–1.86 (2H, m, 2-H, 6-H), 1.74–1.63 (2H, m, 4-H, 10-H_A), 1.46 (1H, ddq, *J* 10.1, 10.1, 6.5, 8-H), 1.43 (3H, s, C(CH_3)CH_3), 1.41 (3H, s, C(CH_3)CH_3), 1.42–1.33 (1H, m, 10-H_B), 1.33 (3H, s, C(CH_3)CH_3), 1.31 (3H, s, C(CH_3)CH_3), 0.99 (3H, d, *J* 7.6, 6-Me), 0.97 (3H, d, *J* 7.1, 2-Me), 0.91 (3H, t, *J* 7.4, 10-Me), 0.76 (3H, d, *J* 6.5, 4-Me), 0.75 (3H, d, *J* 6.5, 8-Me); δ_C (100 MHz; $CDCl_3$) 97.3, 97.2, 77.9, 76.2, 75.5, 75.5, 68.1, 38.2, 35.2, 34.6, 32.8, 30.1, 30.1, 25.9, 19.7, 19.7, 12.5, 11.9, 10.7, 9.4, 9.0; *m*/*z* (CI) 373 (MH^+, 80%), 315 (100), 257 (92), 157 (69); HRMS (CI) Calc. for $C_{21}H_{41}O_5$ (MH^+) 373.2954. Found 373.2954.

(2*S*,3*R*,4*R*,5*R*,6*S*,7*R*,8*R*,9*R*)-3,5:7,9-Bis(isopropylidenedioxy)-2,4,6,8-tetramethylundecanal 17

To a stirred solution of oxalyl chloride (55 μL, 0.63 mmol) in CH_2Cl_2 (1.1 cm^3) at −78 °C was added DMSO (78 μL, 1.10 mmol) and the mixture stirred for 15 min. The alcohol **36** (60.0 mg, 0.16 mmol) was added *via* cannula in CH_2Cl_2 (1.1 cm^3) and the resultant solution stirred at −78 °C for 30 min. Et_3N (0.29 cm^3, 2.09 mmol) was added and stirring continued at −78 °C for 30 min and at −41 °C for 15 min. The reaction was partitioned between NH_4Cl solution (20 cm^3) and CH_2Cl_2 (3 × 40 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (15% EtOAc–hexane) gave the aldehyde **17** (58.4 mg, 98%) as a colourless oil; $[a]_D^{20}$ +16.1 (*c* 3.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 2989vs, 2938vs, 2878s, 2851m, 2714w (C*H*O), 1734vs (C=O); δ_H (400 MHz; $CDCl_3$) 9.63 (1H, s, C*H*O), 4.09 (1H, dd, *J* 10.3, 2.6, 3-H), 3.62 (1H, dd, *J* 10.2, 2.0, 5-H or 7-H), 3.59 (1H, dd, *J* 10.3, 1.7, 5-H or 7-H), 3.37 (1H, ddd, *J* 10.2, 8.0, 2.6, 9-H), 2.50 (1H, dq, *J* 7.0, 2.6, 2-H), 1.94–1.86 (1H, m, 6-H), 1.74 (1H, ddq, *J* 10.3, 10.3, 6.6, 4-H), 1.72–1.63 (1H, m, 10-H_A), 1.46 (1H, ddq, *J* 10.2, 10.2, 6.7, 8-H (Part. obs.)), 1.41 (3H, s, C(CH_3)CH_3), 1.39 (3H, s, C(CH_3)CH_3), 1.41–1.33 (1H, m, 10-H_B (Part. obs.)), 1.33 (3H, s, C(CH_3)CH_3), 1.25 (3H, s, C(CH_3)CH_3), 1.09 (3H, d, *J* 7.0, CHCH_3), 0.99 (3H, d, *J* 7.6, CHCH_3), 0.91 (3H, t, *J* 7.4, 10-Me), 0.80 (3H, d, *J* 6.6, CHCH_3), 0.75 (3H, d, *J* 6.5, CHCH_3); δ_C (100 MHz; $CDCl_3$) 204.8, 97.5, 97.2, 76.1, 75.5, 75.3, 73.7, 47.2, 38.4, 35.2, 32.4, 30.1, 29.7, 25.9, 19.7, 19.5, 12.5, 12.0, 10.8, 9.4, 6.2.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*,12*R*,13*R*)-1-Benzyloxy-7,9:11,13-bis(isopropylidenedioxy)-2,4,6,8,10,12-hexamethylpentadecane-3,5-diol 18

To a stirred solution of (*c*-Hex)$_2$BCl (0.11 cm^3, 0.49 mmol) and Et_3N (68 μL, 0.49 mmol) in Et_2O (2.7 cm^3) at −78 °C was added *via* cannula a solution of ketone (*R*)-**7** (75.5 mg, 0.37 mmol) in Et_2O (1.5 cm^3). The resultant solution was stirred for 0.5 h at −78 °C and 1 h at 0 °C. After recooling to −78 °C, a solution of aldehyde **17** (83.5 mg, 0.23 mmol) in Et_2O (0.5 cm^3) was added *via* cannula and stirring continued at this temperature for 0.5 h and at 0 °C for 1 h. The solution was then recooled to −78 °C and a precooled (−78 °C) solution of $LiBH_4$ (0.7 cm^3 of a 2 M THF solution, 1.35 mmol) added *via* cannula. After 2 h at this temperature, the solution was partitioned between NH_4Cl solution (30 cm^3) and Et_2O (3 × 40 cm^3). The combined organics were washed with H_2O (20 cm^3), concentrated *in vacuo* and oxidised according to procedure B. Flash chromatography (8% EtOAc–hexane) yielded the diol **18** as an oil (96.2 mg, 74%); $[a]_D^{20}$ −2.8 (*c* 3.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3461br (OH), 2968vs, 2937vs, 2855s; δ_H (500 MHz; $CDCl_3$) 7.38–7.24 (5H, m, Ar*H*), 4.87 (1H, s, O*H*), 4.57 and 4.51 (2H, AB_q, *J* 12.0, CH_2Ph), 4.29 (1H, s, O*H*), 3.78–3.70 (3H, m, 3-H, 5-H, 7-H), 3.64–3.55 (3H, m, 9-H, 11-H, 1-H_A), 3.41 (1H, dd, *J* 8.9, 6.9, 1-H_B), 3.37 (1H, ddd, *J* 10.1, 7.9, 2.6, 13-H), 2.03–1.95 (2H, m, 2-H, 6-H), 1.93–1.87 (1H, m, 10-H), 1.80–1.63 (3H, m, 4-H, 8-H, 14-H_A), 1.46 (3H, s, C(CH_3)CH_3), 1.48–1.43 (1H, m, 12-H (Obscured)), 1.42 (3H, s, C(CH_3)CH_3), 1.42–1.34 (1H, m, 14-H_B (Part. obs.)), 1.34 (3H, s, C(CH_3)CH_3), 1.33 (3H, s, C(CH_3)CH_3), 0.99 (3H, d, *J* 7.5, 10-Me), 0.93–0.90 (9H, m, 2-Me, 6-Me, 14-Me), 0.77 (6H, d, *J* 6.4, 8-Me, 12-Me), 0.73 (3H, d, *J* 6.8, 4-Me); δ_C (100 MHz; $CDCl_3$) 138.8, 128.2, 127.6, 127.3, 97.6, 97.2, 83.5, 81.3, 76.1, 76.0, 75.4, 75.4, 74.3, 73.2, 38.2, 38.1, 35.9, 35.2, 33.8, 32.7, 30.1, 30.0, 25.8, 19.7, 19.6, 13.1, 12.4, 11.9, 10.7, 9.3, 9.3, 4.8; *m*/*z* (CI) 579 (MH^+, 11%), 521 (12), 371 (15), 196 (58), 157 (55), 139 (57), 111 (55), 108 (100); HRMS (CI) Calc. for $C_{34}H_{59}O_7$ (MH^+) 579.4261. Found 579.4260.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*,10*S*,11*R*,12*R*,13*R*)-1-Benzyloxy-3,5:7,9:11,13-tris(isopropylidenedioxy)-2,4,6,8,10,12-hexamethylpentadecane 19

Diol **18** (70.1 mg, 0.12 mmol) was stirred in dimethoxypropane (0.74 cm^3, 6.1 mmol) and CH_2Cl_2 (0.74 cm^3). PPTS (5 mg) was added and the mixture stirred for 5 h. Addition of solid $NaHCO_3$ (5 mg), concentration *in vacuo* and flash chromatography (5% Et_2O–hexane) gave the triacetonide **19** (72.3 mg, 97%) as a colourless oil; $[a]_D^{20}$ −7.7 (*c* 4.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 2988s, 2936s, 2877s, 1733w; δ_H (500 MHz; $CDCl_3$) 7.35–7.25 (5H, m, Ar*H*), 4.52 and 4.48 (2H, AB_q, *J* 12.1, CH_2Ph), 3.66 (1H, dd, *J* 10.3, 1.7, 3-H), 3.56–3.53 (4H, m, 5-H, 7-H, 9-H, 11-H), 3.47 (1H, dd, *J* 8.6, 8.6, 1-H_A), 3.38–3.33 (1H,

m, 13-H), 3.30 (1H, dd, *J* 8.6, 6.4, 1-H_B), 2.12–2.06 (1H, m, 2-H), 1.94–1.87 (2H, m, 6-H, 10-H), 1.72–1.63 (3H, m, 4-H, 8-H, 14-H_A), 1.52–1.44 (1H, m, 12-H), 1.40 (3H, s, C(CH_3)-CH_3), 1.41–1.33 (1H, m, 14-H_B (Obscured)), 1.39 (3H, s, C(CH_3)-CH_3), 1.36 (3H, s, C(CH_3)CH_3), 1.34 (3H, s, C(CH_3)CH_3), 1.29 (3H, s, C(CH_3)CH_3), 1.28 (3H, s, C(CH_3)CH_3), 0.98 (6H, d, *J* 7.4, 2 × CHCH_3), 0.92 (3H, t, *J* 7.3, 14-Me), 0.85 (3H, d, *J* 6.9, 2-Me), 0.79 (3H, d, *J* 6.5, CHCH_3), 0.77 (3H, d, *J* 7.0, CHCH_3), 0.75 (3H, d, *J* 6.6, CHCH_3); δ_C (100 MHz; $CDCl_3$) 138.8, 128.2, 127.5, 127.3, 97.2, 97.1, 96.8, 76.4, 76.1, 76.0, 75.9, 75.5, 73.3, 73.2, 73.0, 38.2, 38.1, 35.3, 33.9, 32.7, 32.5, 30.1, 30.1, 30.0, 25.8, 20.0, 19.6, 19.6, 13.4, 12.5, 11.8, 10.3, 10.3, 9.5, 9.3; *m*/*z* (CI) 619 (MH^+, 16%), 603 (15), 503 (52), 486 (26), 446 (43), 428 (39); HRMS (CI) Calc. for $C_{37}H_{63}O_7$ (MH^+) 619.4574. Found 619.4570.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*,10*S*,11*R*,12*R*,13*R*)-1-Benzyloxy-2,4,6,8,10,12-hexamethylpentadecane-3,5,7,9,11,13-hexol 5

Triacetonide **19** (69.0 mg, 0.11 mmol) was heated under reflux with Dowex-50 [85 mg moist, washed with HCl (1 M, 3 × 2 cm^3), H_2O (3 × 2 cm^3) and MeOH (4 × 2 cm^3)] in MeOH (1.1 cm^3) and H_2O (0.12 cm^3). After 4 h the resultant white solid was dissolved and filtered through Celite with the aid of MeOH (30 cm^3) and azeotroped with toluene (3 × 5 cm^3). Flash chromatography (40% EtOAc–hexane) yielded the hexol **5** as a white solid (49.4 mg, 89%); $[a]_D^{20}$ +7.7 (*c* 2.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3374br (OH), 2959vs, 2928s, 2872s; δ_H (500 MHz; C_6D_6) 7.35–7.15 (5H, m, Ar*H*), 6.07 (1H, s, C_7- or C_9-O*H*), 5.85 (1H, s, C_5-O*H*), 5.82 (1H, s, C_7- or C_9-O*H*), 5.72 (1H, s, C_{11}-O*H*), 4.50 (1H, s br, C_{13}-O*H*), 4.48 (1H, s br, C_3-O*H*), 4.34 and 4.30 (2H, AB_q, *J* 12.0, CH_2Ph), 4.00–3.96 (1H, app dd, *J* Obs, 1.5, 7-H or 9-H), 3.97–3.95 (1H, app dd, *J* Obs, 1.3, 11-H), 3.92 (1H, app dd, *J* 9.4, 1.2, 7-H or 9-H), 3.89 (1H, app dd, *J* 9.3, 1.7, 5-H), 3.88–3.85 (1H, m, 3-H), 3.77–3.75 (1H, m, 13-H), 3.47 (1H, dd, *J* 8.9, 5.3, 1-H_A), 3.47 (1H, dd, *J* 8.9, 4.5, 1-H_B), 1.93 (1H, ddq, *J* 9.1, 9.1, 6.8, 8-H), 1.90–1.72 (6H, m, 12-H, 4-H, 10-H, 2-H, 6-H, 14-H_A), 1.60–1.51 (1H, m, 14-H_B), 1.22 (3H, t, *J* 7.3, 14-Me), 1.15 (3H, d, *J* 7.0, 10-Me), 1.10 (3H, d, *J* 6.9, 6-Me), 1.04 (3H, d, *J* 7.0, 2-Me), 0.70 (3H, d, *J* 6.9, 12-Me), 0.60 (3H, d, *J* 6.8, 8-Me), 0.55 (3H, d, *J* 6.9, 4-Me); δ_C (62.5 MHz; $CDCl_3$) 137.7, 128.5, 127.9, 127.6, 83.7, 83.1, 83.0, 83.0, 80.4, 77.5, 75.9, 73.6, 40.1, 38.0, 38.0, 35.1, 35.1, 35.1, 27.3, 13.2, 13.1, 12.8, 9.4, 9.1, 4.3, 4.2; *m*/*z* (FAB) 521 (MNa^+, 35%), 499 (MH^+, 100); HRMS (FAB) Calc. for $C_{28}H_{51}O_7$ (MH^+) 499.3635. Found 499.3672.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*)-1-Benzyloxy-2,4,6,8-tetramethylundecane-3,5,7,9-tetrol 32

Diol **16** (32.0 mg, 0.076 mmol) was heated to reflux with Dowex-50 [40 mg moist, washed with HCl (1 M, 3 × 2 cm^3), H_2O (3 × 2 cm^3) and MeOH (4 × 2 cm^3)] in MeOH (1.1 cm^3) and H_2O (0.12 cm^3). After 1 h further MeOH (1.0 cm^3), H_2O (0.1 cm^3) and Dowex-50 (40 mg) were added and reflux continued for a total of 20 h. The resultant solution was filtered through Celite with the aid of MeOH (45 cm^3) and azeotroped with toluene (3 × 4 cm^3). Flash chromatography (45% EtOAc–hexane) yielded the tetrol **32** as a white solid (22.0 mg, 76%); $[a]_D^{20}$ +9.2 (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3387br (OH), 2434s, 2400s, 1522s; δ_H (500 MHz; C_6D_6) 7.35–7.28 (5H, m, Ar*H*), 5.63 (1H, s, O*H*), 5.42 (1H, s, O*H*), 4.32 and 4.28 (2H, AB_q, *J* 12.0, CH_2Ph), 4.22 (1H, s, O*H*), 4.13 (1H, s, O*H*), 3.88 (1H, app dd, *J* 9.4, 1.3, C*H*OH), 3.84 (1H, app dd, *J* 9.0, 1.8, C*H*OH), 3.80 (1H, app dd, *J* 9.4, <1.0, C*H*OH), 3.75–3.70 (1H, m, C*H*OH), 3.43–3.37 (2H, m, CH_2OBn), 1.89–1.70 (5H, m, 5 × C*H*CH_3), 1.58–1.48 (1H, m, 10-H_B), 1.20 (3H, t, *J* 7.4, 10-Me), 1.12 (3H, d, *J* 7.0, CHCH_3), 1.03 (3H, d, *J* 7.0, CHCH_3), 0.68 (3H, d, *J* 6.9, CHCH_3), 0.53 (3H, d, *J* 6.6, CHCH_3); δ_C (62.5 MHz; $CDCl_3$) 137.7, 128.5, 127.9, 127.6, 83.1, 83.0, 80.7, 77.4, 76.0, 73.7, 40.2, 38.0, 35.2, 35.1, 27.3, 13.2, 12.9, 9.4, 9.1, 4.2; *m*/*z* (FAB) 383 (MH^+, 82%), 307 (21); HRMS (FAB) Calc. for $C_{22}H_{39}O_5$ (MH^+) 383.2797. Found 383.2791.

(2*R*,3*R*,4*R*,5*R*)-1-Benzyloxy-2,4-dimethylheptane-3,5-diol 21

To a stirred solution of $Me_4NBH(OAc)_3$ (4.70 g, 17.9 mmol) in CH_3CN (15 cm^3) at RT was added AcOH (15 cm^3) and the mixture stirred for 30 min. Following cooling to −25 °C, a solution of aldol product **20** (483 mg, 1.83 mmol) in CH_3CN (7 cm^3) was added *via* cannula. After 30 min at this temperature the reaction was transferred to the freezer for 13 h. The solution was poured into potassium sodium tartrate solution (100 cm^3; 0.5 M aq.), stirred for 30 min and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organics were washed with $NaHCO_3$ solution (50 cm^3) and dried ($MgSO_4$). Evaporation *in vacuo* and flash chromatography (10% Et_2O–hexane) gave the product **21** (443 mg, 91%) as a white solid; mp 48–50 °C (pentane); R_t 26.7 min (35% EtOAc–hexane); $[a]_D^{20}$ −37.6 (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3455br (OH); δ_H (400 MHz; $CDCl_3$) 7.39–7.25 (5H, m, Ar*H*), 4.57 and 4.51 (2H, AB_q, *J* 11.8, CH_2Ph), 4.14 (1H, s, O*H*), 3.92–3.87 (1H, m, C*H*OH), 3.63 (1H, dd, *J* 9.0, 4.2, 1-H_A), 3.51 (1H, dd, *J* 9.0, 9.0, 1-H_B), 3.51–3.45 (1H, m, C*H*OH), 3.24 (1H, s, O*H*), 2.08–1.96 (1H, m, C*H*CH_3), 1.68–1.50 (3H, m, 3 × C*H*CH_3), 1.02 (3H, d, *J* 7.0, CHCH_3), 0.97 (3H, t, *J* 7.4, 6-Me), 0.75 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 137.4, 128.4, 127.9, 127.7, 77.5, 76.8, 76.4, 73.5, 37.6, 35.7, 28.5, 12.9, 10.6, 10.4; *m*/*z* (CI) 267 (MH^+, 100%), 196 (43); HRMS (CI) Calc. for $C_{16}H_{27}O_3$ (MH^+) 267.1960. Found 267.1960.

(2*R*,3*R*,4*R*,5*R*)-1-Benzyloxy-3,5-{[bis(1,1-dimethylethyl)-silylene]dioxy}-2,4-dimethylheptane 37

To a stirred solution of diol **21** (67.8 mg, 0.25 mmol) and 2,6-lutidine (0.12 cm^3, 109 mg, 1.02 mmol) in CH_2Cl_2 (0.5 cm^3) was added $(Bu^t)_2Si(OTf)_2$ (0.12 cm^3, 0.38 mmol). After 21 h the resultant solution was quenched with $NaHCO_3$ solution (10 cm^3) and extracted with CH_2Cl_2 (4 × 30 cm^3). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (3% EtOAc–hexane) to yield the product **37** as a colourless oil (85.8 mg, 83%); $[a]_D^{20}$ +37.1 (*c* 2.2, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2969s, 2934s, 2859s, 1476s; δ_H (400 MHz; $CDCl_3$) 7.39–7.25 (5H, m, Ar*H*), 4.56 and 4.50 (2H, AB_q, *J* 11.9, CH_2Ph), 4.04 (1H, dd, *J* 9.7, 2.5, 3-H), 3.78–3.73 (1H, m, 5-H), 3.70 (1H, dd, *J* 8.6, 3.0, 1-H_A), 3.57 (1H, dd, *J* 8.6, 6.3, 1-H_B), 1.93–1.82 (1H, m, C*H*CH_3), 1.76–1.64 (2H, m, 2 × C*H*CH_3), 1.62–1.48 (1H, m, C*H*CH_3), 1.11 (3H, d, *J* 7.4, CHCH_3), 1.06 (9H, s, Si(C(CH_3)$_3$), 1.03 (9H, s, Si(C(CH_3)$_3$), 0.97 (3H, t, *J* 7.3, 6-Me), 0.92 (3H, d, *J* 6.8, CHCH_3); δ_C (100 MHz; $CDCl_3$) 138.9, 128.2, 127.6, 127.3, 81.7, 73.1, 72.6, 72.3, 37.3, 37.1, 31.3, 28.2, 27.9, 22.0, 21.4, 13.6, 13.5, 10.4; *m*/*z* (CI) 407 (MH^+, 91%), 317 (40), 299 (23); HRMS (CI) Calc. for $C_{24}H_{43}O_3Si$ (MH^+) 407.2981. Found 407.2981.

(2*R*,3*R*,4*R*,5*R*)-3,5-{[Bis(1,1-dimethylethyl)silylene]dioxy}-2,4-dimethylheptan-1-ol 22

To a stirred solution of the benzyl ether **37** (481 mg, 1.18 mmol) in EtOH (15 cm^3) was added 10% Pd/C (0.24 g) and the mixture stirred under a hydrogen atmosphere for 3 h. The catalyst was removed by filtration through Celite and the solvent concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc–hexane) yielded the product **22** (364 mg, 97%) as a colourless oil; $[a]_D^{20}$ +19.3 (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3479br (OH), 3016s, 3009s, 2971vs, 2935vs; δ_H (400 MHz; $CDCl_3$) 4.10 (1H, dd, *J* 9.8, 2.5, 3-H), 3.78–3.70 (3H, m, 1-H_A, 1-H_B, O*H*), 3.63–3.55 (1H, m, 5-H), 2.03–1.92 (1H, m, C*H*CH_3), 1.71–1.62 (2H, m, 2 × C*H*CH_3), 1.58–1.45 (1H, m, C*H*CH_3), 1.14 (3H, d, *J* 7.4, CHCH_3), 1.08–1.02 (18H, m, 2 × Si(C(CH_3)$_2$), 0.96 (3H, t, *J* 7.3, 6-Me), 0.71 (3H, d, *J* 6.9,

CHCH_3); δ_C (100 MHz; $CDCl_3$) 81.4, 79.1, 69.5, 37.6, 37.5, 31.3, 28.1, 27.9, 22.1, 21.4, 13.7, 13.1, 10.3; *m/z* (CI) 317 (MH^+, 53%); HRMS (CI) Calc. for $C_{17}H_{37}O_3Si$ (MH^+) 317.2510. Found 317.2512.

(2*S*,3*S*,4*R*,5*R*)-3,5-{[Bis(1,1-dimethylethyl)silylene]dioxy}-2,4-dimethylheptanal 38

To a stirred solution of oxalyl chloride (70 μL, 0.80 mmol) in CH_2Cl_2 (1.4 cm^3) at −78 °C was added DMSO (0.10 cm^3, 1.40 mmol). After 5 min the alcohol **22** (65.2 mg, 0.21 mmol) was added *via* cannula in CH_2Cl_2 (1.4 cm^3) and stirring continued for 30 min. Et_3N (0.37 cm^3, 2.68 mmol) was added dropwise and the mixture stirred for 15 min at −78 °C and at −41 °C for 15 min. The reaction was quenched with NH_4Cl solution (10 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and triturated with cold pentane. Filtration through Celite with hexane (30 cm^3) and evaporation *in vacuo* gave the semi-crude aldehyde as a pale yellow oil (65.9 mg): R_f 0.57 (20% EtOAc–hexane). This compound was prone to elimination and was used *immediately* and without purification in subsequent aldol reactions.

(2*R*,4*R*,5*R*,6*R*,7*R*,8*R*,9*R*)-1-Benzyloxy-5-hydroxy-7,9-{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8-tetramethylundecan-2-one 23

To a stirred solution of (*c*-Hex)$_2$BCl (0.13 cm^3, 0.62 mmol) in Et_2O (2.5 cm^3) was added Et_3N (86 μL, 0.62 mmol) and the mixture was cooled to 0 °C. The ketone (*R*)-**7** (128 mg, 0.62 mmol) in Et_2O (1.6 cm^3) was added *via* cannula and the reaction mixture stirred for 2 h at 0 °C. After cooling to −78 °C a solution of aldehyde **38** (65.9 mg, 0.21 mmol) in Et_2O (0.9 cm^3) was added *via* cannula and stirring continued for 0.45 h before warming to 0 °C. The reaction mixture was partitioned between Et_2O (3 × 15 cm^3) and pH 7 buffer solution (10 cm^3), the organic extracts were combined and concentrated *in vacuo* to give an oil. This residue was oxidised according to procedure A. Flash chromatography (8% EtOAc–hexane) gave the aldol product **23** (77.0 mg, 72%) as a colourless oil; $[\alpha]_D^{20}$ +31.2 (*c* 5.2, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3450br (OH), 1707vs (C=O); δ_H (400 MHz; $CDCl_3$) 7.37–7.25 (5H, m, Ar*H*), 4.53 and 4.47 (2H, AB_q, *J* 12.3, CH_2Ph), 4.43–4.38 (1H, m, 5-H), 4.21 (1H, dd, *J* 9.3, 2.3, 7-H), 3.79–3.75 (1H, m, 9-H), 3.70 (1H, dd, *J* 8.8, 8.8, 1-H_A), 3.40 (1H, dd, *J* 8.8, 4.7, 1-H_B), 3.19–3.10 (1H, m, 2-H), 2.94 (1H, d, *J* 4.6, O*H*), 2.85 (1H, dq, *J* 9.6, 7.0, 4-H), 1.79–1.63 (3H, m, 3 × C*H*CH$_3$), 1.59–1.48 (1H, m, C*H*CH$_3$), 1.10 (3H, d, *J* 7.4, CHCH_3), 1.08–1.00 (24H, m, 2 × CHCH_3, Si(C(CH_3)$_3$)$_2$), 0.97 (3H, t, *J* 7.3, 10-Me), 0.77 (3H, d, *J* 7.0, CHCH_3); δ_C (100 MHz; $CDCl_3$) 217.4, 137.5, 128.4, 127.7, 127.6, 82.0, 73.3, 72.2, 71.8, 70.7, 50.8, 44.2, 37.5, 37.2, 31.2, 28.3, 27.8, 22.0, 21.3, 14.3, 13.6, 13.0, 10.5, 8.5; *m/z* (CI) 521 (MH^+, 4%), 315 (91), 257 (28), 224 (100), 207 (58); HRMS (CI) Calc. for $C_{30}H_{53}O_5Si$ (MH^+) 521.3662. Found 521.3660.

(2*R*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*,9*R*)-1-Benzyloxy-7,9-{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8-tetramethylundecane-3,5-diol 39

To a stirred solution of $Me_4NBH(OAc)_3$ (81.9 mg, 3.1 mmol) in CH_3CN (3.0 cm^3) at RT was added AcOH (3.0 cm^3) and the mixture stirred for 30 min. Following cooling to −25 °C, a solution of aldol product **23** (180 mg, 0.35 mmol) in CH_3CN (2.7 cm^3) was added *via* cannula. After 30 min at this temperature the reaction was transferred to the freezer for 43 h. The solution was poured into potassium sodium tartrate solution (35 cm^3; 0.5 M aq.), stirred for 30 min and extracted with CH_2Cl_2 (4 × 30 cm^3). The combined organics were washed with $NaHCO_3$ solution (30 cm^3) and dried ($MgSO_4$). Evaporation *in vacuo* and flash chromatography (10% EtOAc–hexane) gave the product **39** as a colourless oil (136 mg, 75%); $[\alpha]_D^{20}$ +2.5 (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3474br (OH); δ_H (500 MHz; $CDCl_3$) 7.38–7.26 (5H, m, Ar*H*), 4.56 and 4.52 (2H, AB_q, *J* 11.9, CH_2Ph), 4.19 (1H, dd, *J* 8.8, 2.4, OC*H*), 4.15–4.10 (1H, m, OC*H*), 3.94–3.87 (1H, m, OC*H*), 3.82 (1H, s, O*H*), 3.79–3.75 (1H, m, OC*H*), 3.62 (1H, dd, *J* 8.8, 4.3, 1-H_A), 3.58 (1H, dd, *J* 8.8, 8.8, 1-H_B), 2.73 (1H, d, *J* 4.8, O*H*), 2.10–1.98 (1H, m, C*H*CH$_3$), 1.80–1.64 (4H, m, 4 × C*H*CH$_3$), 1.61–1.49 (1H, m, C*H*CH$_3$), 1.11 (3H, d, *J* 7.3, CHCH_3), 1.08–1.02 (18H, m, Si(C(CH_3)$_3$)$_2$), 0.96 (3H, t, *J* 7.3, 10-Me), 0.86 (3H, d, *J* 6.9, CHCH_3), 0.81 (3H, d, *J* 7.0, CHCH_3), 0.80 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 137.6, 128.5, 127.8, 127.7, 82.0, 76.7, 76.3, 73.5, 73.2, 71.9, 38.5, 37.9, 37.7, 35.9, 31.2, 28.3, 27.9, 22.1, 21.4, 13.8, 13.2, 10.5, 9.9, 9.5; *m/z* (CI) 523 (MH^+, 100%); HRMS (CI) Calc. for $C_{30}H_{55}O_5Si$ (MH^+) 523.3819. Found 523.3820.

(2*R*,3*R*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*)-1-Benzyloxy-3,5:7,9-bis{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8-tetramethylundecane 40

To a stirred solution of diol **39** (95.3 mg, 0.18 mmol) and 2,6-lutidine (0.10 cm^3, 88.0 mg, 0.82 mmol) in CH_2Cl_2 (0.4 cm^3) was added $(Bu^t)_2Si(OTf)_2$ (0.11 cm^3, 0.33 mmol). After 22 h, further 2,6-lutidine (44 μL, 0.36 mmol) and $(Bu^t)_2Si(OTf)_2$ (61 μL, 0.18 mmol) were added. Following 22 h at RT, the resultant solution was quenched with $NaHCO_3$ solution (10 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (8% Et_2O–hexane) to yield the product **40** (71.7 mg, 59%) as a white solid; mp 97–98 °C (pentane); $[\alpha]_D^{20}$ +40.7 (*c* 4.2, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2968vs, 2935vs, 2959vs, 1477vs; δ_H (500 MHz; $CDCl_3$) 7.36–7.22 (5H, m, Ar*H*), 4.53 and 4.48 (2H, AB_q, *J* 12.0, CH_2Ph), 4.36–4.34 (1H, m, OC*H*), 4.20 (1H, dd, *J* 9.7, 1.8, OC*H*), 3.95 (1H, dd, *J* 10.1, 2.9, OC*H*), 3.77 (1H, app t, *J* 6.9, OC*H*), 3.73 (1H, dd, *J* 8.8, 3.0, OC*H*), 3.53–3.48 (1H, m, OC*H*), 1.95–1.85 (1H, m, C*H*CH$_3$), 1.84–1.70 (2H, m, 2 × C*H*CH$_3$), 1.67–1.60 (1H, m, C*H*CH$_3$), 1.59–1.51 (1H, m, C*H*CH$_3$), 1.49–1.40 (1H, m, C*H*CH$_3$), 1.12 (3H, d, *J* 7.4, CHCH_3), 1.10–0.92 (45H, m, 3 × CHCH_3, 2 × Si(C(CH_3)$_3$)$_2$), 0.83 (3H, d, *J* 6.8, CHCH_3); δ_C (100 MHz; $CDCl_3$) 138.9, 128.2, 127.6, 127.3, 82.4, 76.5, 73.7, 73.0, 72.6, 71.0, 45.7, 37.9, 37.1, 36.3, 31.2, 28.2, 27.9, 27.9, 27.7, 22.4, 22.4, 22.1, 21.3, 13.7, 13.7, 13.7, 10.8, 8.9; *m/z* (+FAB, NOBA) 663 (MH^+, 70%), 605 (23), 513 (20), 487 (30), 460 (100); HRMS (+FAB) Calc. for $C_{38}H_{71}O_5Si_2$ (MH^+) 663.4840. Found 663.4785.

(2*R*,3*R*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*)-3,5:7,9-Bis{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8-tetramethylundecan-1-ol 24

To a stirred solution of the benzyl ether **40** (43.1 mg, 0.065 mmol) in EtOH (2.0 cm^3) was added 10% Pd/C (20 mg) and the mixture stirred under a hydrogen atmosphere for 1.5 h. The catalyst was removed by filtration through Celite and the solvent concentrated *in vacuo* to give a colourless oil. Purification by flash chromatography (15% EtOAc–hexane) yielded the product **24** (35.4 mg, 95%) as a white crystalline solid; mp 167–168 °C (pentane); $[\alpha]_D^{20}$ +29.8 (*c* 2.8, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3474br (OH), 2976vs, 2936vs, 2860vs, 1477vs; δ_H (500 MHz; $CDCl_3$) 4.38 (1H, app d, *J* 1.4, OC*H*), 4.20 (1H, dd, *J* 9.7, 2.0, OC*H*), 4.11 (1H, dd, *J* 9.9, 3.0, OC*H*), 3.81–3.73 (3H, m, CH_2OH and CH$_2$O*H*), 3.59 (1H, ddd, *J* 10.5, 10.5, 3.0, 9-H), 2.06–1.97 (1H, m, C*H*CH$_3$), 1.84–1.71 (2H, m, 2 × C*H*CH$_3$), 1.66–1.60 (1H, m, C*H*CH$_3$), 1.60–1.50 (1H, m, C*H*CH$_3$), 1.49–1.40 (1H, m, C*H*CH$_3$), 1.12 (3H, d, *J* 7.5, CHCH_3), 1.10 (3H, d, *J* 7.5, CHCH_3), 1.08–1.02 (36H, m, 2 × Si(C(CH_3)$_3$)$_2$), 0.98 (3H, t, *J* 7.3, 10-Me), 0.82 (3H, d, *J* 6.8, CHCH_3), 0.77 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 82.3, 80.7, 76.4, 70.9, 69.7, 45.7, 38.3, 37.3, 36.3, 31.2, 28.2, 27.9, 27.7, 27.7, 22.5, 22.4, 22.1, 21.3, 13.9, 13.7, 13.2, 10.8, 8.8; *m/z* (FAB) 573 (MH^+, 80%), 515 (25), 397 (62); HRMS (FAB) Calc. for $C_{31}H_{65}O_5Si_2$ (MH^+) 573.4370. Found 573.4314.

(2*S*,3*S*,4*R*,5*R*,6*S*,7*S*,8*R*,9*R*)-3,5:7,9-Bis{[bis(1,1-dimethylethyl)-silylene]dioxy}-2,4,6,8-tetramethylundecanal 41

To a stirred solution of oxalyl chloride (32 μL, 0.36 mmol) in CH_2Cl_2 (0.7 cm^3) at −78 °C was added DMSO (45 μL, 0.63 mmol). After 5 min the alcohol **24** (50.8 mg, 0.09 mmol) was added *via* cannula in CH_2Cl_2 (0.8 cm^3) and stirring continued for 30 min. Et_3N (0.17 cm^3, 1.21 mmol) was added dropwise and the mixture stirred for 15 min at −78 °C and at −41 °C for 15 min. The reaction was quenched with NH_4Cl solution (20 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and triturated with cold pentane. Filtration through Celite with hexane (40 cm^3) gave the semi-crude product aldehyde **41** as a crystalline white solid (54.2 mg): R_f 0.48 (10% EtOAc–hexane). This compound was prone to elimination and was used *immediately* and without purification in subsequent aldol reactions.

(2*R*,4*R*,5*R*,6*R*,7*R*,8*S*,9*R*,10*S*,11*S*,12*R*,13*R*)-1-Benzyloxy-5-hydroxy-7,9:11,13-bis{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8,10,12-hexamethylpentadecan-3-one 42

To a stirred solution of (*c*-Hex)$_2$BCl (59 μL, 0.27 mmol) in Et_2O (1.1 cm^3) was added Et_3N (38 μL, 0.27 mmol) and the mixture was cooled to 0 °C. The ketone (*R*)-**7** (56.0 mg, 0.27 mmol) in Et_2O (0.8 cm^3) was added *via* cannula and the reaction mixture stirred for 1 h at 0 °C. After cooling to −78 °C a solution of aldehyde **41** (49.1 mg, 0.086 mmol) in Et_2O (0.9 cm^3) was added *via* cannula and stirring continued for 1 h before warming to 0 °C for 1.5 h. The reaction mixture was partitioned between Et_2O (3 × 40 cm^3) and pH 7 buffer (20 cm^3), the organic extracts were combined and concentrated *in vacuo* to give an oil. This residue was oxidised according to procedure A. Flash chromatography (8% EtOAc–hexane) gave the aldol **42** (45.0 mg, 67%) as a white solid; R_t 29.7 min (10% EtOAc–hexane); $[\alpha]_D^{20}$ +20.3 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3448br (OH), 2974vs, 2936vs, 2859vs, 1707m (C=O); δ_H (500 MHz; C_6D_6) 7.30–7.25 (5H, m, Ar*H*), 4.80–4.73 (1H, m, 5-H), 4.70–4.66 (1H, m, OC*H*), 4.55–4.49 (2H, m, 2 × OC*H*), 4.37 and 4.32 (2H, AB_q, *J* 12.3, CH_2Ph), 3.86 (1H, dd, *J* 8.4, 5.4, OC*H*), 3.74 (1H, dd, *J* 8.7, 8.7, 1-H_A), 3.24 (1H, dd, *J* 8.7, 4.0, 1-H_B), 3.21 (1H, d, *J* 4.3, O*H*), 3.12–3.03 (1H, m, 2-H), 2.97 (1H, dq, *J* 9.2, 7.3, 4-H), 1.97–1.81 (3H, m, 3 × C*H*CH$_3$), 1.67–1.61 (2H, m, 2 × C*H*CH$_3$), 1.48–1.40 (1H, m, C*H*CH$_3$), 1.36 (9H, s, Si(C(CH_3)$_3$)), 1.35 (9H, s, Si(C(CH_3)$_3$)), 1.32 (9H, s, Si(C(CH_3)$_3$)), 1.31 (9H, s, Si(C(CH_3)$_3$)), 1.24 (3H, d, *J* 7.2, CHCH_3), 1.20 (3H, d, *J* 7.3, CHCH_3), 1.08–1.06 (6H, m, 2 × CHCH_3), 1.02 (3H, d, *J* 6.8, CHCH_3), 0.97 (3H, d, *J* 6.9, CHCH_3), 0.93 (3H, d, *J* 7.0, CHCH_3); δ_C (100 MHz; $CDCl_3$) 217.6, 137.6, 128.4, 127.7, 127.7, 82.4, 76.7, 73.3, 73.2, 72.1, 71.0, 70.6, 50.9, 45.7, 44.1, 38.3, 37.3, 36.3, 31.2, 28.2, 28.0, 27.9, 27.7, 22.4, 22.3, 22.2, 21.3, 14.3, 13.9, 13.7, 13.1, 10.8, 9.0, 8.7; *m*/*z* (FAB) 777 (MH^+, 26%), 759 (8), 719 (15), 601 (30), 513 (74); HRMS (FAB) Calc. for $C_{44}H_{81}O_7Si_2$ (MH^+) 777.5521. Found 777.5538.

(2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,9*S*,10*S*,11*S*,12*R*,13*R*)-1-Benzyloxy-7,9:11,13-bis{[bis(1,1-dimethylethyl)silylene]dioxy}-2,4,6,8,10,12-hexamethylpentadecane-3,5-diol 25

To a stirred solution of $Me_4NBH(OAc)_3$ (81.6 mg, 0.31 mmol) in CH_3CN (0.3 cm^3) at RT was added AcOH (0.3 cm^3) and the mixture stirred for 30 min. Following cooling to −30 °C, a solution of aldol product **42** (26.3 mg, 0.035 mmol) in CH_3CN (0.6 cm^3) and AcOH (0.6 cm^3) was added *via* cannula. After 15 min at this temperature the reaction was transferred to the freezer for 44 h. The solution was poured into potassium sodium tartrate solution (15 cm^3; 0.5 M aq.), stirred for 30 min and extracted with CH_2Cl_2 (4 × 30 cm^3). The combined organics were washed with $NaHCO_3$ solution (30 cm^3) and dried ($MgSO_4$). Evaporation *in vacuo* and flash chromatography (12% EtOAc–hexane) gave the product **25** as a colourless oil (24.1 mg, 90%); $[\alpha]_D^{20}$ +15.5 (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3469br (OH), 3010s, 2973vs, 2934vs, 2859vs, 1477vs; δ_H (500 MHz; $CDCl_3$) 7.39–7.23 (5H, m, Ar*H*), 4.56 and 4.52 (2H, AB_q, *J* 11.9, CH_2Ph), 4.37 (1H, app s, OC*H*), 4.21 (1H, app d, *J* 8.5, OC*H*), 4.18–4.11 (2H, m, 2 × OC*H*), 3.88 (1H, app d, *J* 9.2, OC*H*), 3.80–3.74 (2H, m, OC*H*, O*H*), 3.62 (1H, dd, *J* 8.9, 4.2, 1-H_A), 3.54 (1H, dd, *J* 8.9, 8.9, 1-H_B), 2.73 (1H, dd, *J* 4.3, O*H*), 2.08–1.98 (1H, m, C*H*CH$_3$), 1.83–1.71 (4H, m, 4 × C*H*CH$_3$), 1.67–1.60 (1H, m, C*H*CH$_3$), 1.59–1.52 (1H, m, C*H*CH$_3$), 1.46–1.40 (1H, m, C*H*CH$_3$), 1.12 (3H, d, *J* 7.3, CHCH_3), 1.07–1.03 (39H, m, 4 × Si(C(CH_3)$_3$) and CHCH_3), 0.97 (3H, t, *J* 7.3, 14-Me), 0.88 (3H, d, *J* 6.5, CHCH_3), 0.86 (3H, d, *J* 6.8, CHCH_3), 0.84 (3H, d, *J* 7.0, CHCH_3), 0.81 (3H, d, *J* 6.9, CHCH_3); δ_C (100 MHz; $CDCl_3$) 137.6, 128.5, 127.8, 127.7, 82.4, 77.2, 77.1, 76.4, 74.6, 73.5, 71.8, 71.1, 45.7, 38.8, 38.3, 37.9, 36.3, 35.9, 31.2, 28.2, 28.0, 27.9, 27.8, 22.5, 22.4, 22.2, 21.3, 14.1, 13.7, 13.2, 10.8, 10.1, 9.8, 9.0; *m*/*z* (FAB) 779 (MH^+, 27%), 585 (14), 513 (67), 473 (33); HRMS (FAB) Calc. for $C_{44}H_{83}O_7Si_2$ (MH^+) 779.5677. Found 779.5695.

(2*R*,3*R*,4*S*,5*S*,6*R*,7*R*,8*R*,9*R*,10*S*,11*S*,12*R*,13*R*)-1-Benzyloxy-2,4,6,8,10,12-hexamethylpentadecane-3,5,7,9,11,13-hexol 6

To a stirred solution of diol **25** (20.0 mg, 0.026 mmol) in THF (0.5 cm^3) was added HF·pyridine–pyridine solution (150 μL of stock solution¶). After 14 h at RT, $NaHCO_3$ (40 mg) and silica gel (50 mg) were added and the slurry concentrated *in vacuo*. Flash chromatography (10% MeOH–CH_2Cl_2) gave the hexol **6** as a white solid (10.1 mg, 79%); $[\alpha]_D^{20}$ −6.3 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3420br (OH), 2985vs, 2940s, 2881m; δ_H (500 MHz; CD_3OD) 7.37–7.20 (5H, m, Ar*H*), 4.52 (2H, s, CH_2Ph), 4.05–3.95 (4H, m, 4 × C*H*OH), 3.88 (1H, app dd, *J* 9.8, 1.2, C*H*OH), 3.70 (1H, dd, *J* 9.0, 4.5, 1-H_A), 3.56 (1H, dd, *J* 9.0, 6.4, 1-H_B), 3.51–3.48 (1H, m, C*H*OH), 1.94–1.86 (1H, m, C*H*CH$_3$), 1.79–1.56 (6H, m, 6 × C*H*CH$_3$), 1.53–1.43 (1H, m, C*H*CH$_3$), 0.98 (3H, t, *J* 7.4, 14-Me), 0.92 (3H, d, *J* 6.8, CHCH_3), 0.92 (3H, d, *J* 7.0, CHCH_3), 0.81–0.73 (12H, m, 4 × CHCH_3); δ_C (62.5 MHz; CD_3OD) 137.0, 126.4, 125.9, 125.7, 74.3, 72.7, 71.4, 70.7, 70.2, 69.5, 69.1, 69.1, 37.2, 36.1, 36.1, 36.1, 35.7, 35.4, 25.6, 11.5, 7.8, 7.3, 6.4, 6.4, 6.4, 6.2; *m*/*z* (FAB) 521 (MNa^+, 47%), 499 (MH^+, 100); HRMS (FAB) Calc. for $C_{28}H_{51}O_7$ (MH^+) 499.3635. Found 499.3670.

(2*S*,4*S*,5*S*,6*R*,7*S*,8*R*,9*R*)-1-Benzyloxy-5-hydroxy-7,9-isopropylidenedioxy-2,4,6,8-tetramethylundecan-3-one 26

To a stirred solution of (*c*-Hex)$_2$BCl (0.65 cm^3, 3.0 mmol) in Et_2O (12 cm^3) was added Et_3N (0.42 cm^3, 3.0 mmol) and the mixture was cooled to −78 °C. The ketone (*S*)-**7** (0.62 g, 3.0 mmol) in Et_2O (5 cm^3) was added *via* cannula and the reaction mixture stirred for 1.5 h at −78 °C and at −5 °C for 30 min. After recooling to −78 °C, a solution of the aldehyde **15** (0.21 g, 1.0 mmol) in Et_2O (2.4 cm^3) was added *via* cannula and stirring continued at −78 °C for 0.75 h at −5 °C for 1.5 h. The reaction mixture was partitioned between Et_2O (3 × 50 cm^3) and pH 7 buffer solution (35 cm^3), the organic extracts were combined, washed with H_2O (50 cm^3) and concentrated *in vacuo* to give an oil. This residue was oxidised according to procedure A. Flash chromatography (15% EtOAc–hexane) yielded the aldol products (0.33 g, 79%). HPLC (15% EtOAc–hexane) of a portion of this material yielded the minor diastereomers (17.6 mg) and major isomer **26** (96.9 mg) as a colourless oil (85% diastereoselection); R_t 25.2 min (15% EtOAc–hexane); $[\alpha]_D^{20}$ +46.9 (*c* 2.3, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3499br (OH), 2972s, 2877s, 1714s (C=O); δ_H (500 MHz; C_6D_6) 7.34–7.10 (5H, m, Ar*H*), 4.38 and 4.32 (2H, AB_q, *J* 12.0, CH_2Ph), 3.97 (1H, dd, *J* 10.2, 1.9, 7-H), 3.90 (1H, m, 5-H), 3.69 (1H, dd, *J* 8.6, 8.6, 1-H_A), 3.69 (1H, d, *J* 9.6, O*H*), 3.41 (1H, dd, *J* 8.6, 5.3, 1-H_B), 3.33–3.26 (1H, m,

¶ Stock solution prepared from pyridinium hydrofluoride (2.1 g) in THF (20 ml) and pyridine (7.0 ml).

9-H), 3.20–3.10 (1H, m, 2-H), 3.13 (1H, dq, *J* 7.1, 7.1, 4-H), 1.84–1.80 (1H, m, 6-H), 1.64–1.58 (1H, m, 10-H_A), 1.56 (1H, ddq, *J* 10.2, 10.2, 6.6, 8-H), 1.46 (3H, s, C(CH_3)CH_3), 1.44 (3H, s, C(CH_3)CH_3), 1.45–1.36 (1H, m, 10-H_B (Part. obs.)), 1.21 (3H, d, *J* 6.9, 2-Me), 1.17 (3H, d, *J* 7.1, 4-Me), 1.12 (3H, d, *J* 7.1, 6-Me), 1.07 (3H, t, *J* 7.4, 10-Me), 0.47 (3H, d, *J* 6.6, 8-Me); δ_C (100 MHz; $CDCl_3$) 217.4, 138.1, 128.2, 127.5, 127.5, 97.8, 78.7, 75.4, 74.2, 73.2, 72.6, 49.2, 47.8, 34.4, 33.4, 30.1, 25.7, 19.7, 13.5, 12.9, 11.4, 10.5, 9.2; *m*/*z* (CI) 438 (M + NH_4^+, 6%), 421 (MH^+, 13), 345 (11), 224 (78), 215 (28), 207 (33), 157 (32), 139 (100), 108 (15); HRMS (CI) Calc. for $C_{25}H_{41}O_5$ (MH^+) 421.2954. Found 421.2954.

(2*R*,4*R*,5*R*,6*R*,7*S*,8*R*,9*R*)-1-Benzyloxy-4-ethyl-5-hydroxy-7,9-isopropylidenedioxy-2,6,8-trimethylundecan-3-one 28

To a stirred solution of (*c*-Hex)$_2$BCl (0.94 cm^3, 4.36 mmol) in Et_2O (17 cm^3) was added Et_3N (0.61 cm^3, 4.36 mmol) and the mixture was cooled to 0 °C. The ketone (*R*)-**27** (0.96 g, 4.36 mmol) in Et_2O (6.3 cm^3) was added *via* cannula and the reaction mixture stirred for 1.5 h at 0 °C for 30 min. After cooling to −78 °C a solution of the aldehyde **15** (0.34 g, 1.45 mmol) in Et_2O (4.7 cm^3) was added *via* cannula and stirring continued at −78 °C for 0.75 h and at 0 °C for 1.5 h. The reaction mixture was partitioned between Et_2O (3 × 50 cm^3) and pH 7 buffer solution (30 cm^3), the organic extracts were combined and concentrated *in vacuo* to give an oil. This residue was oxidised according to procedure A. Flash chromatography (10% EtOAc–hexane) gave the aldol **28** (0.59 g, 93%) as a colourless oil; $[a]_D^{20}$ −15.3 (*c* 2.3, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3488br (OH), 3024vs, 2937vs, 2877vs, 1708vs (C=O); δ_H (500 MHz; $CDCl_3$) 7.33–7.23 (5H, m, Ar*H*), 4.51 and 4.47 (2H, AB_q, *J* 12.0, CH_2Ph), 3.89 (1H, app d, *J* 9.1, 5-H), 3.73–3.68 (2H, m, 1-H_A, 7-H), 3.46 (1H, dd, *J* 9.2, 5.7, 1-H_B), 3.43 (1H, d, *J* 1.0, O*H*), 3.42–3.36 (1H, m, 9-H), 3.05–2.95 (1H, m, 2-H), 2.83 (1H, ddd, *J* 9.1, 9.1, 4.1, 4-H), 1.86–1.80 (1H, m, 6-H), 1.71–1.63 (1H, m, 10-H_A), 1.62–1.48 (2H, m, 8-H, C_4-C$H_A$$H_B$$CH_3$), 1.43 (3H, s, C(C$H_3$)$CH_3$), 1.43–1.33 (2H, m, 10-$H_B$, C_4-$CH_A$$H_B$$CH_3$), 1.33 (3H, s, C($CH_3$)-C$H_3$), 1.12 (3H, d, *J* 7.0, 2-Me), 0.94 (3H, d, *J* 6.9, 6-Me), 0.92 (3H, t, *J* 7.4, 10-Me), 0.83 (3H, t, *J* 7.5, C_4-CH_2CH_3), 0.73 (3H, d, *J* 6.7, 8-Me); δ_C (100 MHz; $CDCl_3$) 216.8, 138.1, 128.2, 127.5, 127.4, 98.0, 80.2, 78.2, 75.1, 73.1, 71.6, 54.9, 48.4, 34.7, 33.8, 29.9, 25.7, 21.6, 19.7, 13.0, 11.6, 11.4, 9.3, 5.0; *m*/*z* (CI) 452 (M + NH_4^+, 13%), 435 (MH^+, 23), 238 (100), 221 (33); HRMS (CI) Calc. for $C_{26}H_{43}O_5$ (MH^+) 435.3111. Found 435.3110.

Acknowledgements

This paper is dedicated to the memory of Professor Ralph A. Raphael—mentor, colleague and friend. We thank Professor R. W. Hoffmann (Marburg) for helpful discussions. This work was supported by the EPSRC (GR/L22560, Quota Studentship to J. P. S.), the EU TMR programme (ERB-FMRX-CT96-0011), Novartis AG (Basel), Merck Sharp & Dohme, Pfizer Central Research and the Newton Trust (Cambridge).

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