Stereocontrol in organic synthesis using silicon-containing compounds. A synthesis of nonactin

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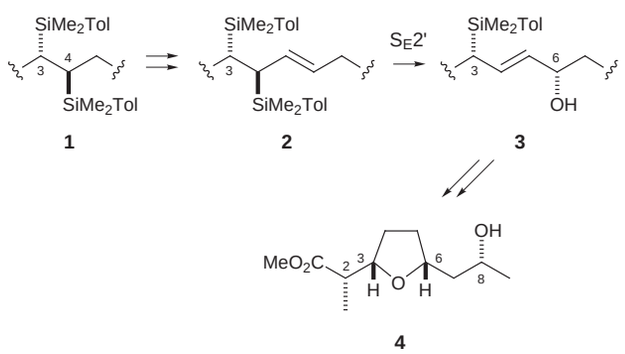
The enantiomeric purity of (1*R*)-1-(1′-naphthyl)ethanol 7 was raised by Horeau's method by separating its oxalate 11 from its diastereoisomer by crystallisation. The alcohol 7 was used to open the anhydride of (3*RS*,4*SR*)-3,4-bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid with selectivity of 96 : 4 for one of the enantiotopic carbonyl groups, allowing the synthesis of (3*R*,4*S*)-3,4-bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid 6-(2-trimethylsilylethyl) ester 10. This acid was converted into the allylsilane methyl (*E*)-(3*S*,4*R*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-7-(2-methyldioxolan-2-yl)hept-5-enoate 15, the carboxylic acid derived from which underwent epoxidation with unexpected silyl migration to give (3*S*,4*S*,5*S*,6*R*)-3,5-bis[dimethyl(4-methylphenyl)silyl]-6-hydroxy-7-(2-methyldioxolan-2-yl)heptano-4-lactone 17. Desilylative elimination and hydrogenation then gave the alcohol (3*R*,6*R*)-3-[dimethyl(4-methylphenyl)silyl]-6-hydroxy-7-(2-methyldioxolan-2-yl)heptanoic acid 19, in which the relative and absolute configuration at C-3 and C-6 have been controlled. The relative configuration at C-8 was controlled by *anti*-selective reduction of a 6-hydroxy-8-ketone using Evans' method, and at C-2 by *anti*-selective enolate methylation of the β-silyl lactone 20. Silyl-to-hydroxy conversion with retention at C-3 and displacement of the tosylate with inversion at the same centre gave the correct relative and absolute configuration, completing a synthesis of methyl (+)-nonactate 4. The relative configuration at C-8 was controlled in the opposite sense by *syn*-selective reduction of a 6-hydroxy-8-ketone using Prasad's conditions, and at C-2 in the opposite sense by *anti*-selective enolate methylation of the open-chain β-silyl ester 22. Silyl-to-hydroxy conversion with retention at C-3 and displacement of the tosylate with inversion at C-6 gave the correct relative and absolute configuration completing a synthesis of the pseudo-enantiomer, benzyl (−)-nonactate 25. Some protecting group changes and coupling of these two fragments gave the "dimers" 28 and 29, coupling of which gave the "tetramer" 30. Ring closure of this material using Yamaguchi's method gave nonactin in 73% yield, substantially better than in any previous synthesis.

Introduction

In the preceding paper we described our first synthesis of methyl (+)-nonactate **4**.[1] As in all our syntheses, the methods for stereocontrol were versatile, and could have been adapted to the synthesis of its enantiomer, which would be needed if we were to put the two together in a synthesis of nonactin **31**. However, we had also developed a versatile synthon **5** with two silyl groups 1,2-related on a functionalised 6-carbon chain,[2] and we were anxious to demonstrate how versatile that intermediate was. Rather than continue the work described in the preceding paper, we chose to use the diester **5**, with its well controlled pair of stereocentres, and report here how we have been able to synthesise nonactate esters in both enantiomeric series—methyl (+)-nonactate **4** and benzyl (−)-nonactate **25**—and hence nonactin itself. This work was the subject of three preliminary communications,[3,4] and 44 lectures, one of which was published.[5]

As discussed in the preceding paper, the central problem with using our silicon-based methods of stereocontrol in a synthesis of nonactate is the 1,4-relationship between C-3 and C-6, since we already have well developed methods for dealing with the 1,2-relationship between C-2 and C-3, and the 1,3-relationship between C-6 and C-8. The idea for setting up the 1,4-related centres from a starting material **1** with 1,2-related centres was to use the S_E2' reaction of an allylsilane **2** to move the stereochemical information three atoms along the chain, changing the 1,2-relationship in the starting material into a 1,4-relationship in the product **3** (Scheme 1). Since what we wanted was an oxygen atom on C-6, we used the epoxidation of an allylsilane, a reaction that we and others had shown already to be well controlled stereochemically when the carbon substituent C-3 on the stereogenic centre in the allylsilane **2** was branched,[6,7] as it is here.

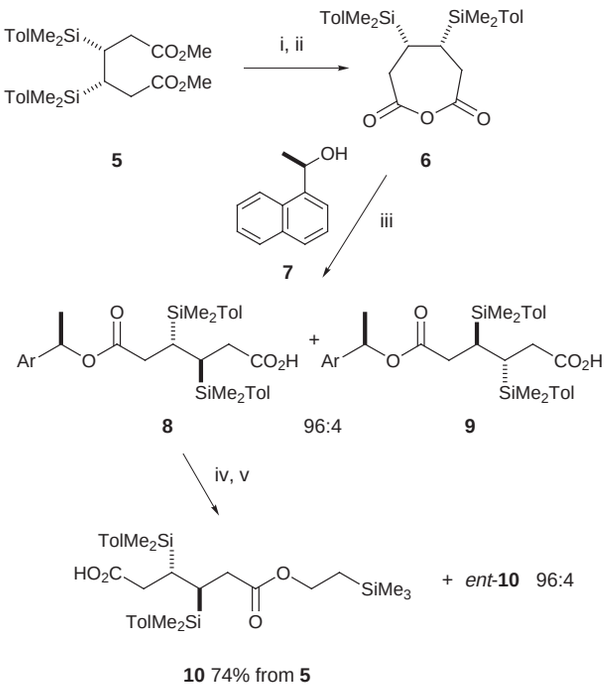


Scheme 1

Results and discussion

We developed the synthesis of the two nonactate esters **4** and **25** using racemic material, before we repeated it with enantiomerically enriched material. In order to save repeating ourselves, we shall simply describe the synthesis of the enantiomerically enriched esters, and will give the results from our work in the racemic series in the experimental section only when they add data like melting points that are not the same as they are for the enantiomerically enriched compounds.

In order to make enantiomerically enriched material from the *meso* diester **5**, we needed to differentiate the enantiotopic ester groups. Although we tried a few esterases on the ester and on the dicarboxylic acid derived from it, success came from a

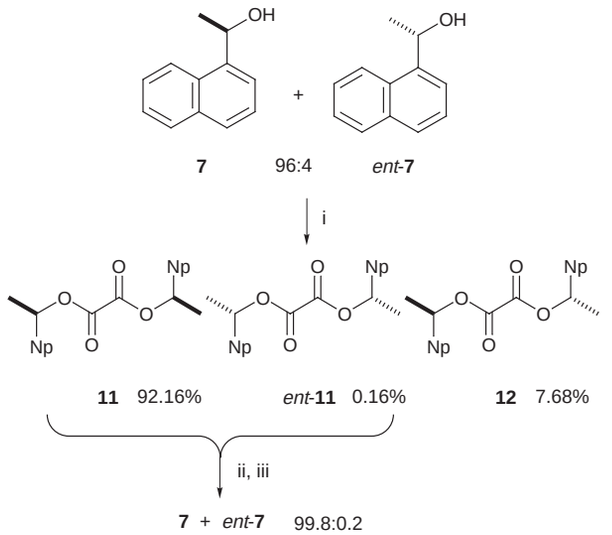


Scheme 2 *Reagents*: i, LiOH; ii, DCC; iii, DMAP; iv, $HOCH_2CH_2SiMe_3$, DCC, DMAP; v, H_2, Pd/C

chemical method, in which we opened the *meso* anhydride **6** with Heathcock's naphthalene alcohol **7**.[8] Using racemic alcohol, we could see (^{1}H NMR spectroscopy) that the inseparable racemic diastereoisomers **8** and **9** were present in a ratio of 96:4. With enantiomerically pure naphthalene alcohol, we should therefore obtain, after esterifying the free carboxylic acid group and removing the chiral auxiliary by hydrogenolysis, the mono ester **10** contaminated with only 4% of its enantiomer, which we judged would be good enough to start with, and which might be improved along the way. We therefore needed the enantiomerically pure alcohol **7**, and so we repeated Theisen and Heathcock's enzymatic esterification procedure[8] for preparing it. Unfortunately, we obtained the alcohol contaminated with 4% of its enantiomer, as measured using a chiral GC column. In view of the impending loss of another 4% of enantiomeric control in the next step, we feared that this material might not be good enough, and so we turned to a method by which we might improve it using an idea of Horeau's.[9]

We treated the 96:4 mixture of alcohols **7** and *ent*-**7** with oxalyl chloride and obtained a mixture of the three possible diesters **11**, *ent*-**11** and **12** in 100% yield. Assuming that there is no chiral recognition, the statistical probability for the formation of these isomers is given by the numbers $(0.96)^2$:$(0.04)^2$:$(2 \times 0.96 \times 0.04)$, which means that we can expect 92.16% of **11**, 0.16% of *ent*-**11** and 7.68% of **12** (Scheme 3). The *R*,*R* and *S*,*S* diesters **11** and *ent*-**11** could be separated easily from their diastereoisomer **12**, because they crystallised. The ester **12** remained as an oil, and we deliberately gave it no opportunity to crystallise. Recrystallisation gave the esters **11** and *ent*-**11** free of the diastereoisomer **12**, as judged by the ^{1}H NMR spectrum. Two further recrystallisations gave material with an overall yield of 78%.

Alkaline hydrolysis of this mixture of esters **11** and *ent*-**11**, gave the mixture of alcohols **7** and *ent*-**7** in a ratio of 99.8:0.2, identical within experimental error to the statistical ratio. Like Theisen and Heathcock, we also recovered from the enzymatic reaction a mixture rich (94:6) in the enantiomeric alcohol *ent*-**7**. Mitsunobu reaction on this alcohol using *p*-nitrobenzoic acid,[10] and alkaline hydrolysis of the derived ester gave another mixture of the alcohols **7** and *ent*-**7**, rich (90:10) in the desired enantiomer **7**. We were able to repeat the same procedure as in Scheme 3 using oxalyl chloride with this inferior material, and

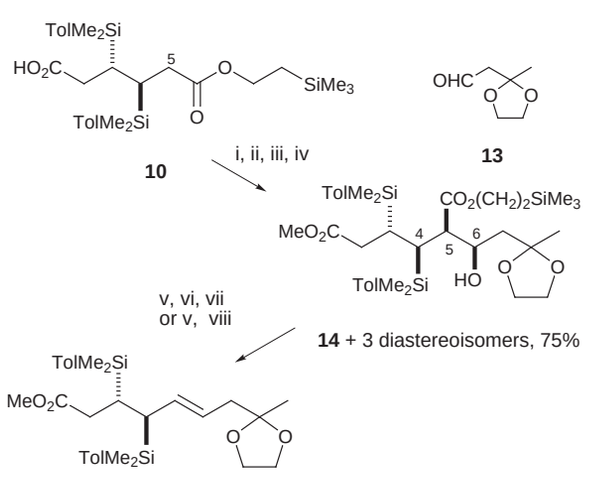


Scheme 3 *Reagents*: i, $(COCl)_2$, Py, DMAP; ii, separate from **12** by crystallisation; iii, KOH, EtOH

obtained, after six recrystallisations, followed by alkaline hydrolysis, another crop of alcohol **7** with the enantiomers in a ratio of 99.8:0.2. By combining the two crops, we obtained the alcohol **7** in 44% actual yield from the racemic mixture. Since we also recovered 23% of racemic alcohol, the overall yield is 57%. Our preliminary communciation[3] gives a little more of the algebra for Horeau's method of enhancing enantiomeric purity, and some extensions of it have been fully discussed by Rautenstrauch.[11] We believe that we are the first to have put the full potential of Horeau's idea to use in a total synthesis.

We repeated the reaction with the anhydride **6** using the enantiomerically enriched alcohol, and obtained the inseparable diastereoisomeric esters **8** and **9** in a ratio of 96:4, as before. Esterification and hydrogenolysis, therefore, gave the homochiral mono ester **10** contaminated with 4% of its enantiomer. At this stage, of course, we did not know which enantiomer we had. Heathcock's substrate was a 3-substituted glutaric anhydride, and it did not have *C*-silyl groups, let alone two of them. Nevertheless, by analogy with his results, we tentatively assumed that the enantiomer we had produced was that with the absolute configuration **10**, and this was eventually confirmed when we reached the first known compound, methyl (+)-nonactate **4**.

Using one of our allylsilane syntheses,[12] we converted the ester **10** into the *E*-allylsilane **15** (Scheme 4). In order to extend

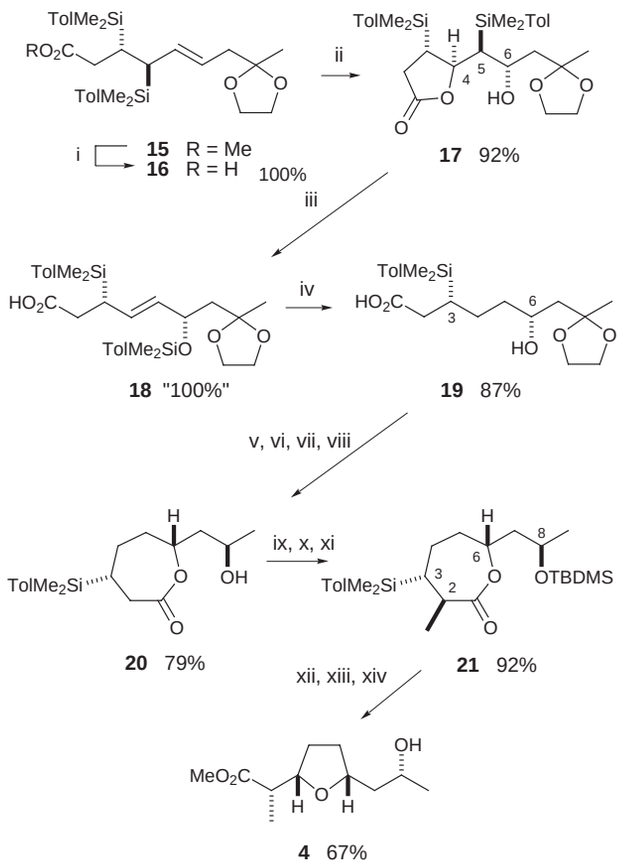


Scheme 4 *Reagents*: i, 2 LDA, THF, DMPU; ii, **13**; iii, CH_2N_2; iv, separate diastereoisomers; v, TBAF; vi, $PhSO_2Cl$, Py; vii, collidine, reflux; viii, $Me_2NCH(OCH_2Bu^t)_2$, heat

the chain from C-5, we needed to carry out an aldol reaction without incurring Dieckmann cyclisation. We avoided this pitfall, by leaving C-1 as an unprotected carboxylic acid group, and using two equivalents of base, one to make the carboxylate ion and the other to make the enolate at C-5. Aldol condensation with Kelly's aldehyde **13**[13] and esterification with diazomethane gave largely the diastereoisomer **14**, together with all three other diastereoisomers in a ratio of 76:9:9:6. We were able to separate them into three fractions, with the 76% and the 6% eluting together from the chromatographic column. We removed the silylethyl group from them all. We treated the acid derived from the mixed fraction with benzenesulfonyl chloride to make the β-lactone, at which stage, by good luck, we were able to separate it from the 6% product that had not undergone hydrolysis or β-lactone formation as fast as the major product. We heated the β-lactone derived from the major product to induce a *syn* stereospecific decarboxylative elimination, and obtained the *E*-allylsilane **15**, showing that this product had the *syn* relationship between the substituents on C-5 and C-6. When we hydrolysed one of the 9% products and persuaded it to form a β-lactone, it also decarboxylated to form the *E*-allylsilane **15**, showing that this isomer must also have had the *syn* relationship between C-5 and C-6. The two compounds that proved to have the *anti* relationship were the 9% and 6% products. We separately treated the acids derived from each of them with dimethylformamide dineopentyl acetal to induce an *anti* stereospecific decarboxylative elimination, and obtained the same *E*-allylsilane from them both. This is the first time that we have used the full convergent possibilities of this allylsilane synthesis, and the overall yield of the *E*-allylsilane **15** from the ester **10** was a gratifying 68%.

We hydrolysed the combined crops of esters **15** to obtain the acid **16**, which we found to be necessary for a clean reaction in the next stage (Scheme 5). Clean the epoxidation was, with a good yield and essentially complete stereocontrol, as far as we could tell, but we did not isolate an epoxide. Instead, we isolated the lactone **17** as a consequence of silyl migration from C-4 to C-5 with capture of the intermediate cation on C-4 by the carboxylate ion. This reaction resembles somewhat the epoxidation–lactonisation reactions seen by Procter,[7,14] but with the extra feature in our case of a silyl shift. We deduced the relative stereochemistry shown for this intermediate from the expectation that the epoxidation was stereospecifically *anti*[6] in setting up the configuration at C-6, that the silyl group had migrated with inversion of configuration at the migration terminus C-5, and with retention of configuration at the migration origin C-4, as we had seen before in a similar reaction described in the paper earlier in this sequence.[2] The lactone **17** was not the only product; we also separated 3% of a diastereoisomer, which we assume to be that resulting from incomplete stereospecificity in the epoxidation. It almost certainly has the opposite configuration at both C-5 and C-6, and so we discarded it. The selective elimination of the silyl group on C-5 in **17** and the lactone oxygen on C-4 took place on treatment with potassium hydride, with both the chemoselectivity and the stereoselectivity for the *trans* product **15** having good precedent in the work of Yamamoto.[15] Hydrogenation of this alkene to give the key intermediate **19** proved to be difficult, in line with earlier difficulties we have had in trying to hydrogenate allylsilanes. Hydrogenation only took place when we released the C-6 hydroxy group from its *O*-silyl ether, by carrying out the reaction in methanol. At this stage we had controlled the 1,4-related, and well differentiated, centres between C-3 and C-6, in 12 steps, in an overall yield of 40% from the ester **5**.

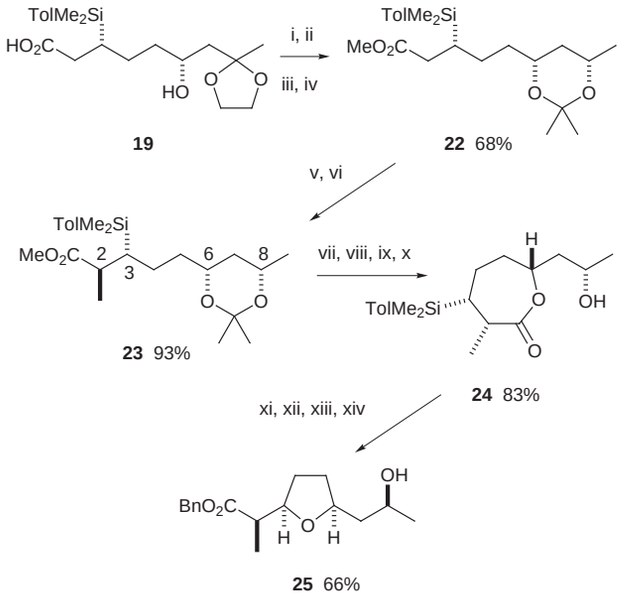
From this branch point, we carried out two sequences to give each of the nonactate esters. In the first (Scheme 5), we used Evans' method[16] for reducing a 3-hydroxy ketone to an *anti* 1,3-diol with high selectivity (*ca.* 95:5). We separated the major product and treated it with Mukaiyama's reagent[17] to give the lactone **20**. At this stage we were able to filter off a small



Scheme 5 *Reagents*: i, KOH; ii, MCPBA, Na_2HPO_4; iii, KH, THF; iv, H_2, PtO_2, MeOH; v, $PyH^+ {}^-OTs$, Me_2CO; vi, $Me_4N^+ {}^-BH(OAc)_3$; vii, 2-chloro-*N*-methylpyridinium iodide, Et_3N; viii, separate from racemate (96:4→99.5:0.5); ix, TBDMSCl, DMF, imidazole; x, LDA, THF, DMPU; xi, MeI; xii, KBr, AcO_2H, NaOAc, AcOH; xiii, TsCl, Py, DMAP; xiv, TsOH, MeOH

amount of the crystalline racemic lactone, and thereby raised the ratio of enantiomers from 96:4 to 99.5:0.5. Protection of the free hydroxy group and enolate methylation gave only the lactone **21** with the *anti* relationship between the silyl and methyl groups. Although most of our work on silicon-controlled enolate alkylations has been with open-chain esters,[18] we have seen a highly diastereoselective methylation of a caprolactone before.[19] The four stereocentres C-2, C-3, C-6 and C-8 were now in place—all that remained was to convert the silyl to a hydroxy group,[20] to tosylate the new hydroxy group, and open the lactone, whereupon cyclisation took place with inversion of configuration at C-3 to give methyl (+)-nonactate **4**, identifiably the correct diastereoisomer by its definitive[2] ^1H NMR spectrum, and with specific rotation close to that reported.[4] Gas chromatography on a homochiral column confirmed the high enantiomeric purity of this material (99.6:0.4). The overall yield for the 10 steps from the common intermediate **19** to methyl (+)-nonactate **4** was 49%.

In the second sequence (Scheme 6), starting from the common intermediate **19**, we did everything in the opposite sense. We used Prasad's version[21] of Narasaka's method[22] to give the *syn* 1,3-diol (90:10), which we separated from the minor diastereoisomer and protected as its acetonide **22**. We methylated the ester stereoselectively **22**→**23**, following our well established rule for the alkylation of open-chain esters having a β-silyl group.[18] Methylation in an open-chain ester sets up the C-2 and C-3 stereocentres in the opposite sense along the carbon backbone to the methylation of the lactone **20**→**21**, although the cause, electrophilic attack taking place *anti* to the silyl group, is of course the same. Unexpectedly, we only detected a single diastereoisomer **23**, whereas esters having a silyl and a primary alkyl group on the β-stereogenic centre have usually given us



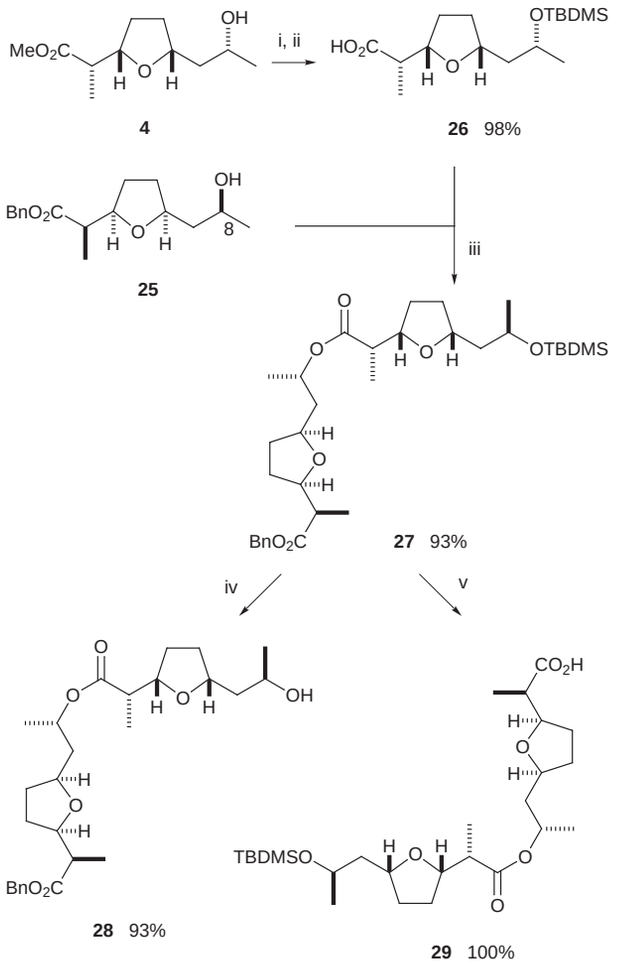
Scheme 6 *Reagents*: i, CH_2N_2; ii, PyH^+ ^-OTs, Me_2CO; iii, $NaBH_4$, Bu_2BOMe; iv, PyH^+ ^-OTs, $Me_2C(OMe)_2$; v, LDA, THF, DMPU; vi, MeI; vii, PyH^+ ^-OTs, MeOH; viii, KOH; ix, 2-chloro-*N*-methylpyridinium iodide, Et_3N; x, separate from racemate (96:4→98:2); xi, TBDMSCl, DMF, imidazole; xii, $NaOCH_2Ph$; xiii, TsCl, Py, DMAP; xiv, KBr, AcO_2H, AcOH

ratios of diastereoisomers of between 80:20 and 90:10. The remaining steps were designed to allow us to tosylate selectively the C-6 hydroxy group, in order to induce inversion of configuration at that centre. Acetal hydrolysis, ester hydrolysis and lactonisation gave the lactone **24**, and again some of the crystalline racemate could be filtered off, raising the ratio of enantiomers from 96:4 to 98:2 or better. Protection of the free hydroxy group and base-catalysed opening of the lactone with benzyl alcohol revealed the C-6 hydroxy group, which we tosylated. Silyl-to-hydroxy conversion[20] allowed the formation, with inversion of configuration at C-6, of benzyl (−)-nonactate **25**. Hydrogenolysis and treatment with diazomethane gave methyl (−)-nonactate, which appeared to be diastereomerically pure in its ^{1}H NMR spectrum, and enantiomerically of higher purity (homochiral GC) than the minimum of 98:2 we had estimated earlier. The overall yield for the 12 steps from the common intermediate **19** to benzyl (−)-nonactate **25** was 35%.

Having demonstrated the versatility of our methods by synthesising both enantiomers in the nonactic acid series, and finding ourselves, for all the length of our synthesis, in possession of adequate material, we were able to complete a synthesis of nonactin itself. Nonactin **31**, in contrast to its subunit nonactic acid, had been synthesised by only three groups before, namely those of Gerlach,[23] Schmidt[24,25] and Bartlett.[26] The overall yield from the nonactic acid esters was low in all of these syntheses, with Bartlett's, the best and most recent, being 10%.

Silylation of the free hydroxy group of the methyl ester **4** and saponification of the ester gave the carboxylic acid **26**, which we coupled to the free hydroxy group of the benzyl ester **25** to give the protected ester **27** (Scheme 7). Removing the silyl protecting group from half of this ester gave the alcohol **28**, and removing the benzyl group from the other half gave the acid **29**.

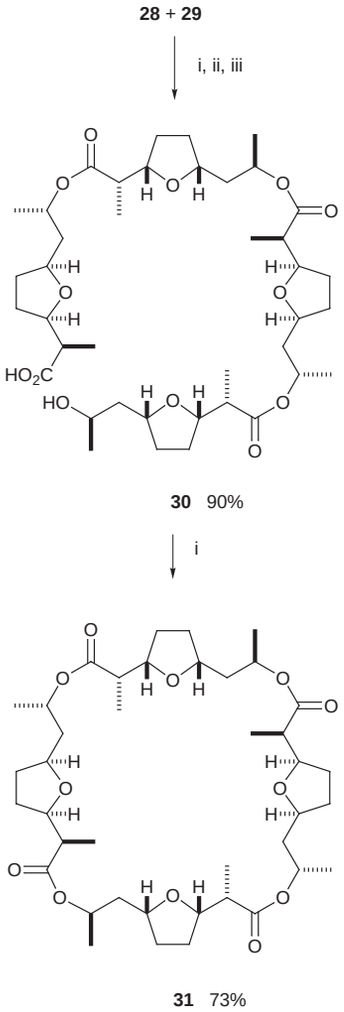
We coupled these two compounds, using Yamaguchi's mixed anhydride method,[27] and removed the remaining protecting groups to give the hydroxy acid **30**. Yamaguchi macrolactonisation gave nonactin **31**, in 73% yield, after recrystallisation, with mp and ^{1}H and ^{13}C NMR data matching those reported by Bartlett.[26] We repeated the macrolactonisation in the presence of potassium fluoroborate (nonactin chelates potassium exceptionally well), in the faint hope that chelation might raise the yield even more, but it had no effect. The overall yield of nonactin from the esters **4** and **25** was 59%.



Scheme 7 *Reagents*: i, TBDMSCl, DMF, imidazole; ii, KOH; iii, DCC, DMAP; iv, TsOH, AcOH, H_2O; v, H_2, Pd/C

The yield in the macrolactonisation step is remarkably high given the number of stereogenic centres among which errors could have accumulated during the synthesis. That we achieved this high yield can probably be credited principally to Yamaguchi's method, but it must also mean that we had components **4** and **25** of high enantiomeric and diastereoisomeric purity, even though we had not been able to recrystallise any of the intermediates in the homochiral series—only the *meso* compounds, our starting material **5** and nonactin itself were usefully crystalline. (There were actually two crystalline intermediates—the alcohol obtained by silyl-to-hydroxy conversion of **21** and the *tert*-butyldimethylsilyl ether of **24**—but both were too soluble in organic solvents for effective recrystallisation.) We had the advantage in our sequence that we did not have to invert the configuration at C-8 in preparing the "dimer" **27**, as both Schmidt and Bartlett did using displacements of tosylate and mesylate groups, respectively. Their operations, if inversion of configuration is not total, are inherently more likely to give mixtures of diastereoisomers than our method, which safely leaves the configuration at this centre undisturbed. We were also able to use the hydrogenolysis of a benzyl ester twice in this sequence, having taken to heart Bartlett's observation that base- or nucleophile-induced ester cleavage caused 20% or more epimerisation at C-2 in the methyl ester corresponding to our intermediate **27**. Although we used dilute solutions for the macrolactonisation (97 mg of **30** in 45 cm^3 of dichloromethane), they were not exceptionally dilute. We conclude that there is no inherent difficulty in closing the macrocyclic ring of nonactin.

We also tried the shorter route using 2 + 2 coupling. We removed both protecting groups from the intermediate **27**, to give the hydroxy acid having ^{1}H and ^{13}C NMR spectra essentially identical with those reported by Bartlett.[3] Using Yamagu-



Scheme 8 *Reagents*: i, 2,4,6-trichlorobenzoyl chloride, DMAP; ii, H_2, Pd/C; iii, TsOH, AcOH, H_2O

chi's conditions again, we carried out the coupling and macrolactonisation in one operation to give nonactin **31** directly, in 52% yield after recrystallisation. As Bartlett found using different macrolactonisation conditions, this sequence detectably gave the lactone of the "dimer" and probably higher oligomeric lactones too, which must account for the lower yield.

In summary, we have demonstrated in this series of papers how versatile our methods are. We acknowledge that many of our syntheses are long, especially the one described in this paper, which must be by far the longest synthesis of nonactin ever carried out, or ever likely to be. We gain high levels of stereocontrol from our methods, high levels of predictability, and the capacity to make any of the diastereoisomers if we choose to aim for them, but we suffer from having to include the steps needed to introduce our control element, and effectively to convert it, like alchemists, into another. The synthesis described in this paper shows our methods at their best and worst—we started with 14 g of the ester **5** and finished, after 43 steps with 100 mg of nonactin.

Experimental

General

The synthetic route, as far as the two nonactate esters **4** and **25**, was worked out with racemic compounds. Up to that point in the synthesis, most of the analytical and spectroscopic data were collected for the corresponding racemic compound, but the yields and procedures described are those used in the enantiomerically enriched series.

Bis[(*R*)-(1′-naphthyl)ethyl] oxalate 11

Oxalyl chloride (4.58 cm^3, 51.5 mmol), the alcohol **7**[8] (96:4 ratio of enantiomers by GC, 17.67 g, 102.7 mmol) and 4-dimethylaminopyridine (1.5 g, 12.3 mmol) were stirred in pyridine (20 cm^3) and dichloromethane (180 cm^3) at room temperature for 3 h. The mixture was poured into water and extracted with chloroform (2 × 100 cm^3). The extract was washed with dilute hydrochloric acid (3 mol dm^{-3} in H_2O), with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *oxalate* (20.42 g, 100%); mp 120–123 °C. The crude oxalate (20.42 g) recrystallised from hexane (1200 cm^3) gave oxalate {18.486 g, 90.5%, mp 122–124 °C, $[\alpha]_D^{20}$ −28.93 (*c* 1.03 in $CHCl_3$)}; this oxalate (18.386 g) from cyclohexane (300 cm^3) gave oxalate {16.715 g, 91%, (82.4% overall) mp 123–124 °C, $[\alpha]_D^{20}$ −30.14 (*c* 1.05 in $CHCl_3$)}; and this oxalate (16.71 g) from cyclohexane (160 cm^3) gave *oxalate* {15.765 g, 94.4% (78% overall), mp 123–25 °C, $[\alpha]_D^{20}$ −30.3 (*c* 0.99 in $CHCl_3$)}; R_f (EtOAc–hexane, 10:90) 0.15; ν_{max}(film)/cm^{-1} 1760 (C=O), 1740 (C=O) and 1600 (Ar); δ_H(250 MHz; $CDCl_3$) 8.11–8.05 (2 H, m, Ar), 7.91–7.80 (4 H, m, Ar), 7.65–7.42 (8 H, m, Ar), 6.75 (2 H, q, *J* 6.6, 2 × MeC*H*OCO) and 1.80 (6 H, d, *J* 6.6, *Me*C-CHOCO) (Found: C, 78.22; H, 5.48. $C_{26}H_{22}O_4$ requires C, 78.37; H, 5.57%).

(*R*)-1-(1′-Naphthyl)ethanol 7

Potassium hydroxide (1 mol dm^{-3} in H_2O–EtOH, 4:96, 160 cm^3) and the oxalate **11** (15.554 g, 39 mmol) were stirred at 17 °C for 2.5 h. The solvent was evaporated under reduced pressure. The residue was diluted with ice cold water (200 cm^3) and extracted with ether (3 × 150 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to give the alcohol (13.44 g, 100%); bp 109–110 °C at 0.09 mmHg; $[\alpha]_D^{20}$ +87.94 (*c* 1 in Et_2O) {lit.,[8] $[\alpha]_D^{25}$ +82.1 (*c* 0.95 in Et_2O)}; R_f (EtOAc–hexane, 25:75) 0.25. GC [β-cyclodextrin (CYDEX-B), 25 m, 0.25 micron film thickness, He carrier; conditions: 150 °C for 5 min, then 2 °C min^{-1} up to 200 °C, t_R 22.942 min for (*S*)-isomer and 23.217 min for (*R*)-isomer] showed the enantiomers to be present in the ratio 99.8:0.2.

(*R*)-1-(1′-Naphthyl)ethyl 4-nitrobenzoate

Diethyl azodicarboxylate (17.3 cm^3, 110 mmol) was added dropwise to a stirred suspension of the (*S*)-1-(1′-naphthyl)-ethanol *ent*-**7** isolated from the enzymatic digestion[8] (ratio of enantiomers 94:6, 9.57 g, 55 mmol), triphenylphosphine (29 g, 110 mmol) and 4-nitrobenzoic acid (18.44 g, 110 mmol) in toluene (275 cm^3) under nitrogen at 0 °C, and kept for 1.5 h at room temperature. The solvent was removed under reduced pressure and the residue was triturated with ether–hexane (1:1) and filtered. The filtrate was washed with aqueous sodium hydroxide (10%) and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 5:95) to give the *ester* (16.24 g, 92%); R_f (EtOAc–hexane, 10:90) 0.2; $[\alpha]_D^{17}$ −95.73 (*c* 1.27 in ether); ν_{max}(film)/cm^{-1} 1710 (C=O) and 1600 (Ar); δ_H(250 MHz; $CDCl_3$) 8.31–8.22 (4 H, m, Ar), 8.18–8.14 (1 H, m, Ar), 7.91–7.82 (2 H, m, Ar), 7.70–7.67 (1 H, m, Ar), 7.60–7.46 (3 H, m, Ar), 6.90 (1 H, q, *J* 6.6, CHOCO) and 1.88 (3 H, d, *J* 6.6, *Me*CHOCO); *m*/*z* 321 (82%, M^+), 155 (100, Naph-CHMe) and 150 (68, 4-$NO_2C_6H_4CO$) (Found: M^+, 321.0982. $C_{19}H_{15}NO_4$ requires *M*, 321.1001).

(*R*)-1-(1′-Naphthyl)ethanol 7 from its nitrobenzoate

The nitrobenzoate (28.2 g, 87.9 mmol) in THF (25 cm^3) and methanol (25 cm^3) was stirred with sodium hydroxide (0.6 mol dm^{-3} in MeOH, 250 cm^3) at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was taken up in ether (300 cm^3). The ether solution was washed with aqueous sodium hydroxide (10%), with water and with

brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 15:85) to give the alcohol (12.7 g, 84%); bp 109–110 °C/0.09 mmHg; $[\alpha]_D^{20}$ +70.5 (*c* 1.04 in Et_2O); R_f (EtOAc–hexane, 25:75) 0.25. The ratio of enantiomers (GC) was 90:10.

Enantiomer enrichment of the alcohol 7

The oxalate (15.4 g) was made from the alcohol as described above, and recrystallised from hexane giving successively crops of 13.4 g, mp 110–116 °C; 12 g, mp 115–119 °C; 10.9 g, mp 116–122 °C; 9.1 g, mp 122–124 °C; 8.4 g, mp 124–125 °C; 7.7 g (53%) mp 124–125 °C; and 7.1 g (49%); mp 124–125 °C; $[\alpha]_D^{20}$ −30.4 (*c* 1.0 in $CHCl_3$). The alcohol prepared from this ester as described above had a ratio of enantiomers 99.96:0.04.

(3*RS*,4*SR*)-3,4-Bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid

The diester **5** (1.41 g, 3 mmol) in THF (50 cm^3) and methanol (20 cm^3) was kept with lithium hydroxide (1 mol dm^{-3} in H_2O, 20 cm^3) at room temperature for 48 h. The solvent was evaporated under reduced pressure, acidified with ice cold hydrochloric acid (3 mol dm^{-3} in H_2O, 10 cm^3) and extracted with ethyl acetate (3 × 50 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *diacid* (1.31 g, 99%) as needles, mp 166–167 °C (from EtOAc); R_f (EtOAc–hexane, 1:1) 0.25; $\nu_{max}(CHCl_3)/cm^{-1}$ 3300–2500 (CO_2H), 1715 (C=O), 1260 (SiMe) and 1110 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.30 (4 H, d, *J* 7.8, Ar), 7.12 (4 H, d, *J* 7.8, Ar), 2.49 (2 H, dd, *J* 9.1 and 17.0, 2 × $CH_AH_BCO_2H$), 2.38 (2 H, dd, *J* 6.1 and 17, 2 × $CH_AH_BCO_2H$), 2.31 (6 H, s, 2 × 4-MeC_6H_4), 1.83 (2 H, t, *J* 6, 2 × SiCH), 0.24 (6 H, s, 2 × $SiMe_AMe_B$) and 0.23 (6 H, s, 2 × $SiMe_AMe_B$); *m*/*z* 427 (5%, M − Me) and 149 (100, 4-$MeC_6H_4SiMe_2$) (Found: C, 65.22; H, 7.88. $C_{24}H_{34}O_4Si_2$ requires C, 65.11, H, 7.74%).

(3*S*,4*R*)-3,4-Bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid (1*R*)-1-(1′-naphthyl)ethyl ester 8

Dicyclohexylcarbodiimide (2.55 g, 12.4 mmol) in dichloromethane (180 cm^3) was added dropwise over 1.5 h to a stirred solution of the diacid (5.425 g, 12.7 mmol) in dichloromethane (550 cm^3) at 0 °C. After 12 h at room temperature, the mixture was concentrated (to 250 cm^3) and the precipitated dicyclohexylurea was removed by filtration. (*R*)-1-(1′-Naphthyl)ethanol **7** (4.136 g, 24.05 mmol) and 4-dimethylaminopyridine (720 mg, 5.9 mmol) in dichloromethane (50 cm^3) were added dropwise to the filtrate under nitrogen at −78 °C. After 4 days at −30 °C, the mixture was washed with dilute hydrochloric acid and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 20:80) to give the *mono ester* (6.14 g, 84%); $[\alpha]_D^{22}$ +7.4 (*c* 1.06 in MeOH); R_f (EtOAc–hexane, 25:75) 0.27; ν_{max}(film)/cm^{-1} 3400–2500 (br, COOH), 1720 (C=O), 1700 (C=O), 1600 (Ar), 1260 (SiMe) and 1110 (SiAr); δ_H(250 MHz; $CDCl_3$) 8.04–7.99 (1 H, m, Ar), 7.87–7.81 (1 H, m, Ar), 7.77 (1 H, d, *J* 8.0, Ar), 7.54–7.39 (4 H, m, Ar), 7.31–7.26 (4 H, m, Ar), 7.09 (2 H, d, *J* 6.3, Ar), 7.07 (2H, d, *J* 7.4, Ar), 6.52 (1 H, q, *J* 6.6, CHOCO), 2.58–2.33 (4 H, m, 2 × CH_2COO), 2.28 (6 H, s, 2 × 4-MeC_6H_4), 1.93–1.81 (2 H, m, 2 × SiCH), 1.60 (3 H, d, *J* 6.6, *Me*CHOCO), 0.24 (3 H, s, SiMe), 0.22 (6 H, s, 2 × SiMe) and 0.19 (3 H, s, SiMe) (Found: C, 73.02; H, 7.63. $C_{36}H_{44}O_4Si_2$ requires C, 72.44; H, 7.43%). This compound did not give an acceptable combustion analysis after repeated attempts. A sample of the acid (0.05 mmol) was esterified with diazomethane to give the methyl ester; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O), 1600 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) (values for major diastereoisomer only) 8.06–8.01 (1 H, m, Ar), 7.88–7.83 (1 H, m, Ar), 7.79 (1 H, d, *J* 8 Ar), 7.54–7.41 (4 H, m, Ar), 7.30 (4 H, d, *J* 7.9, Ar), 7.10 (2 H, d, *J* 7.9, Ar), 7.07 (2H, d, *J* 7.9, Ar), 6.60 (1 H, q, *J* 6.6, MeC*H*OCO), 3.47 (3 H, s, CO_2Me), 2.58–2.32 (4 H, m, 2 × CH_2COO), 2.29 (6 H, s, 2 × 4-MeC_6H_4), 1.92–1.78 (2 H, m, 2 × SiCH), 1.62 (3 H, d, *J* 6.6, *Me*CHOCO), 0.23 (3 H, s, SiMe), 0.22 (3 H, s, SiMe), 0.20 (3 H, s, SiMe) and 0.19 (3 H, s, SiMe), and with a recognisable peak for the minor diastereoisomer at δ 3.41. The ratio of diastereoisomers was 96:4 (from the integration of the OMe resonances at δ 3.47 and 3.41).

(3*S*,4*R*)-3,4-Bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid 6-(2-trimethylsilylethyl) ester 1-(*R*)-1-(1′-naphthyl)ethyl ester

Dicyclohexylcarbodiimide (5.65 g, 27 mmol) in dichloromethane (40 cm^3) was added dropwise over 1.5 h to a stirred solution of the acid **8** (13.7 g, 23 mmol), 2-trimethylsilylethanol (3.54 g, 30 mmol) and 4-dimethylaminopyridine (690 mg, 5.6 mmol) in dichloromethane (30 cm^3) at 0 °C and the mixture kept at room temperature for 12 h. The solvent was evaporated off, and the residue was diluted with ether (100 cm^3), filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 5:95) to give the *diester* (15.18 g, 95%); $[\alpha]_D^{22}$ +10.82 (*c* 1.16 in MeOH); R_f (EtOAc–hexane, 10:90) 0.34; ν_{max}(film)/cm^{-1} 1720 (C=O), 1600 (Ar), 1260 (SiMe) and 1110 (SiAr); δ_H(250 MHz; $CDCl_3$) 8.06–8.02 (1 H, m, Ar), 7.88–7.84 (1 H, m, Ar), 7.78 (1 H, d, *J* 8, Ar), 7.55–7.41 (4 H, m, Ar), 7.31 (2 H, d, *J* 7.9, Ar), 7.30 (2 H, d, *J* 7.9, Ar), 7.10 (2 H, d, *J* 7.9, Ar), 7.08 (2 H, d, *J* 7.9, Ar), 6.52 (1 H, q, *J* 6.5, CHOCO), 3.99–3.92 (2 H, m, CH_2OCO), 2.59–2.32 (4 H, m, 2 × CH_2COO), 2.29 (6 H, s, 2 × 4-MeC_6H_4), 1.95–1.83 (2 H, m, 2 × SiCH), 1.62 (3 H, d, *J* 6.5, *Me*CHOCO), 0.90–0.83 (2 H, m, $SiCH_2$), 0.25 (3 H, s, SiMe), 0.24 (3 H, s, SiMe), 0.22 (3 H, s, SiMe), 0.20 (3 H, s, SiMe) and 0.01 (9 H, s, $SiMe_3$) (Found: C, 70.76; H, 8.14. $C_{41}H_{56}O_4Si_3$ requires C, 70.64; H, 8.10%).

(3*S*,4*R*)-Bis[dimethyl(4-methylphenyl)silyl]hexane-1,6-dioic acid 6-(2-trimethylsilylethyl) ester 10

Palladium (10% on charcoal) (500 mg) was stirred with the diester (14.62 g, 21 mmol) in ethyl acetate (100 cm^3) under hydrogen for 7 days. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane–AcOH; 14:85:1) to give the *mono ester* (10.7 g, 94%); $[\alpha]_D^{22}$ +2.3 (*c* 1.52 in Et_2O); R_f (EtOAc–hexane, 25:75) 0.30; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500–2500 (br, CO_2H), 1730 (C=O), 1710 (C=O), 1610 (Ar), 1260 (SiMe) and 1110 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.32 (4 H, d, *J* 7.9, Ar), 7.12 (4 H, d, *J* 7.9, Ar), 4.00–3.93 (2 H, m, CO_2CH_2), 2.57–2.34 (4 H, m, 2 × CH_2CO_2), 2.32 (6 H, s, 2 × 4-MeC_6H_4), 1.82 (2 H, t, *J* 6.9, 2 × SiCH), 0.9–0.83 (2 H, m, $SiCH_2$), 0.26 (6 H, s, 2 × SiMe), 0.23 (3 H, s, SiMe), 0.22 (3 H, s, SiMe) and 0.0 (9 H, s, $SiMe_3$); δ_C(100 MHz, $CDCl_3$) 178.54, 173.93, 138.87, 138.78, 134.81, 134.65, 134.16, 134.14, 128.62, 128.57, 62.63, 35.97, 35.74, 23.51, 23.42, 21.44, 17.16, −1.54, −2.29, −2.40, −2.66 and −2.67; *m*/*z* 542 (0.7%, M^+), 541 (1.2, M − H) and 149 (100, 4-$MeC_6H_4SiMe_2$) and 73 (57, $SiMe_3$) (Found: C, 64.15; H, 8.70; M^+, 542.2685. $C_{29}H_{46}O_4Si_3$ requires C, 64.15; H, 8.54%; *M*, 542.2704).

Methyl (3*S*,4*R*,5*R*,6*R*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-5-(2-trimethylsilylethoxycarbonyl)-6-hydroxy-7-(2-methyl-dioxolan-2-yl)heptanoate 14 and its (5*S*,6*S*)-, (5*R*,6*S*)- and (5*S*,6*R*)-diastereoisomers

n-Butyllithium (1.6 mol dm^{-3} in hexane, 14.7 cm^3) was added dropwise to a stirred solution of diisopropylamine (3.4 cm^3, 24 mmol) in dry THF (38 cm^3) under nitrogen at −78 °C. After 20 min at 0 °C, the solution was brought to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-one (19 cm^3) was added followed by the mono ester **10** (5.05 g, 9.317 mmol) in dry THF (19 cm^3) over 15 min. The temperature was raised to −45 °C over 1 h, and maintained at −45 to −50 °C for 1 h. The aldehyde **13**[13] (2.6 g, 20 mmol) in THF (10 cm^3) was added at −78 °C over 10 min and the mixture was stirred for 3 h. The mixture was quenched with saturated aqueous ammonium chloride, acidified with aqueous citric acid (10%) and extracted

with ether (3 × 200 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was esterified with ethereal diazomethane and chromatographed (SiO_2, EtOAc–hexane, 20:80) to give the (5R,6R)-*hydroxy ester* mixed with the (5S,6R)-ester (4.08 g, 61% and 3%); $[\alpha]_D^{20}$ +1.15 (*c* 2.44 in $CHCl_3$); R_f (EtOAc–hexane, 30:70) 0.35; ν_{max}(film)/cm^{-1} 3530 (OH), 1740 (C=O), 1600 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.44 (2 H, d, *J* 7.8, Ar), 7.17 (2 H, d, *J* 7.8, Ar), 7.14 (2 H, d, *J* 7.8, Ar), 7.07 (2 H, d, *J* 7.8, Ar), 4.16–4.07 (2 H, m, CO_2CH_2), 3.91–3.80 (4 H, m, OCH_2CH_2O), 3.77–3.68 (1 H, m, C*H*OH), 3.45 (3 H, s, OMe), 3.06 (1 H, d, *J* 5.3, OH), 2.70–2.45 (3 H, m, CH_2CO_2Me and $CHCO_2$), 2.36 (3 H, s, 4-*Me*C_6H_4), 2.30 (3 H, s, 4-*Me*C_6H_4), 2.0 (1 H, ddd, *J* 1.3, 4.8 and 10.8, SiCH), 1.92 (1 H, dd, *J* 1.3 and 6.5, SiCH), 1.56 (1 H, dd, *J* 2.5, 14.5, C$H_A$$H_B$CHOH), 1.44 (1 H, dd, *J* 9 and 14.5, CH_AH_BCHOH), 1.16 (3 H, s, MeC), 1.02–0.94 (2 H, m, $SiCH_2$), 0.36 (3 H, s, SiMe), 0.34 (3 H, s, SiMe), 0.26 (3 H, s, SiMe), 0.25 (3 H, s, SiMe) and 0.03 (9 H, s, $SiMe_3$) (Found: C, 62.74; H, 8.48. $C_{36}H_{58}O_7Si_3$ requires C, 62.93; H, 8.51%), the (5R,6S)-*hydroxy ester* (400 mg, 6%); $[\alpha]_D^{20}$ +0.35 (*c* 1.44 in $CHCl_3$); R_f (EtOAc–hexane, 30:70) 0.40; δ_H(250 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 7.9, Ar), 7.32 (2 H, d, *J* 7.9, Ar), 7.14 (2 H, d, *J* 7.9, Ar), 7.12 (2 H, d, *J* 7.9, Ar), 4.16–3.97 (3 H, m, C*H*OH, CO_2CH_2), 3.95–3.82 (4 H, m, OCH_2CH_2O), 3.39 (3 H, s, OMe), 3.37 (1 H, d, *J* 1.5, OH), 2.63–2.42 (3 H, m, $CHCO_2$ and CH_2CO_2Me), 2.33 (6 H, s, 2 × 4-*Me*C_6H_4), 2.36–2.25 (1 H, m, SiCH), 2.15 (1 H, d, *J* 3, SiCH), 1.55 (2 H, d, *J* 5.6, CH_2CHOH), 1.23 (3 H, s, MeC), 0.97–0.89 (2 H, m, $SiCH_2$), 0.36 (3 H, s, SiMe), 0.30 (3 H, s, SiMe), 0.27 (3 H, s, SiMe), 0.18 (3 H, s, SiMe) and 0.02 (9 H, s, $SiMe_3$), and the (5S,6S)-*hydroxy ester* (320 mg, 5%); R_f (EtOAc–hexane, 30:70) 0.30; δ_H(250 MHz; $CDCl_3$) 7.45 (2 H, d, *J* 7.9, Ar), 7.18 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 7.07 (2 H, d, *J* 7.9, Ar), 4.29–4.20 (1 H, m, C*H*OH, became ddd, *J* 2.4, 4.5 and 8.5 after D_2O exchange), 4.0–3.8 (4 H, m, OCH_2CH_2O), 3.76–3.55 (2 H, m, CO_2CH_2), 3.44 (3 H, s, OMe), 3.32 (1 H, d, *J* 6.4, OH), 2.60–2.39 (3 H, m, CH_2CO_2Me and $CHCO_2$), 2.35 (3 H, s, 4-*Me*C_6H_4), 2.30 (3 H, s, 4-*Me*C_6H_4), 2.24 (1 H, ddd, *J* 2.5, 6.3 and 8.5, SiCH), 1.98 (1 H, dd, *J* 2.5 and 8.5, SiCH), 1.76 (1 H, dd, *J* 2.5, 14.5, C$H_A$$H_B$CHOH), 1.58 (1 H, dd, *J* 9, 14.5, CH_AH_BCHOH), 1.33 (3 H, s, Me), 0.89–0.80 (2 H, m, CH_2Si), 0.35 (3 H, s, SiMe), 0.31 (6 H, s, 2 × SiMe), 0.26 (3 H, s, SiMe) and 0.00 (9 H, s, $SiMe_3$). The (5S,6R)-*hydroxy ester* (195 mg, 3%); R_f (EtOAc–hexane, 30:70) 0.35; δ_H(250 MHz; $CDCl_3$) 7.37 (2 H, d, *J* 7.9, Ar), 7.31 (2 H, d, *J* 7.9, Ar), 7.11 (4 H, d, *J* 7.9, Ar), 4.14 (1 H, t, *J* 9.4, C*H*OH), 4.03 (1 H, dd, *J* 7.2 and 10.7, C$H_A$$H_B$OCO), 3.97 (1 H, dd, *J* 6.7 and 10.7, CH_AH_BOCO), 3.94–3.83 (4 H, m, OCH_2CH_2O), 3.32 (3 H, s, OMe), 2.86 (1 H, dd, *J* 3.9 and 15.6, C$H_A$$H_B$$CO_2$Me), 2.67 (1 H, dd, *J* 3.7 and 9.4, $CHCO_2$), 2.34 (1 H, dd, *J* 10 and 15.6, $CH_AC$$H_B$$CO_2$Me), 2.32 (3 H, s, 4-*Me*C_6H_4), 2.31 (3 H, s, 4-*Me*C_6H_4), 2.14 (1 H, t, *J* 3.8, SiCH), 1.97 (1 H, t, *J* 3.7, SiCH), 1.85 (1 H, d, *J* 14.2, C$H_A$$H_B$CHOH), 1.56 (1 H, dd, *J* 9.4, 14.2, CH_AH_BCHOH), 1.30 (3 H, s, MeC), 0.96–0.80 (2 H, m, $SiCH_2$), 0.33 (3 H, s, SiMe), 0.32 (3 H, s, SiMe), 0.16 (3 H, s, SiMe), 0.11 (3 H, s, SiMe) and 0.02 (9 H, s, $SiMe_3$) was isolated by chance after deprotection of the 2-trimethylsilylethyl ester and β-lactonisation had selectively removed the major isomer **14**. This isomer was the major product when the aldol reaction was carried out in the absence of DMPU when the same four isomers (30%) were obtained in the ratio 10:12:21:57. The stereochemistry between C-5 and C-6 for each of these isomers follows from the stereochemistry of their decarboxylative elimination reactions, and the stereochemistry between C-4 and C-5 is assumed to have the major product, that with the (5*R*) configuration, for the usual reasons established for aldol reactions of enolates with a β-silyl group.[28]

Methyl (3*S*,4*R*,5*R*,6*R*) 3,4-bis[dimethyl(4-methylphenyl)silyl]-5-carboxy-6-hydroxy-7-(2-methyldioxolan-2-yl)heptanoate

Tetrabutylammonium fluoride (1 mol dm^{-3} in THF, 30 cm^3) was added dropwise with stirring to the hydroxy ester **14** (8.65 g, 12.609 mmol) in dry THF (140 cm^3) under nitrogen at 0 °C, and the mixture stirred for 30 min at room temperature. Crushed ice (200 g) was added to the mixture and the solvent was evaporated under reduced pressure. The mixture was acidified with citric acid solution and extracted with ethyl acetate (2 × 200 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy acid (7.37 g, 100%); $[\alpha]_D^{20}$ +5.41 (*c* 2.18 in $CHCl_3$); R_f (EtOAc) 0.24; ν_{max}($CHCl_3$)/cm^{-1} 3500 (OH), 3600–2500 (br, CO_2H), 1720 (C=O), 1610 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.45 (2 H, d, *J* 7.8, Ar), 7.19 (2 H, d, *J* 7.8, Ar), 7.16–7.0 (4 H, m, Ar), 3.97–3.70 (5 H, m, C*H*OH and OCH_2CH_2O), 3.56 (3 H, s, OMe), 2.71 (1 H, dd, *J* 5 and 15.9, C$H_A$$H_B$$CO_2$Me), 2.60 (1 H, dd, *J* 2.6 and 9.6, C*H*CO_2H), 2.52 (1 H, dd, *J* 10.2 and 15.9, $CH_AC$$H_B$$CO_2$Me), 2.38 (3 H, s, 4-*Me*C_6H_4), 2.29 (3 H, s, 4-*Me*C_6H_4), 2.05 (1 H, dd, *J* 1.4, 9.2, SiCH), 1.94 (1 H, ddd, *J* 1.4, 5 and 10.2, SiCH), 1.74 (1 H, dd, *J* 9.9 and 15, C$H_A$$H_B$CHOH), 1.63 (1 H, dd, *J* 2 and 15, CH_A-H_BCHOH), 1.14 (3 H, s, MeC), 0.37 (3 H, s, SiMe), 0.34 (3 H, s, SiMe), 0.32 (3 H, s, SiMe) and 0.23 (3 H, s, SiMe). The other diastereoisomers were hydrolysed similarly in essentially quantitative yield.

β-Lactone of methyl (3*S*,4*R*,5*R*,6*R*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-5-carboxy-6-hydroxy-7-(2-methyldioxolan-2-yl)-heptanoate

Following Adam,[29] benzenesulfonyl chloride (5.3 cm^3, 41.4 mmol) was added dropwise to a stirred solution of the (5*R*,6*R*)-hydroxy acid (11.46 g, 19.556 mmol) in dry pyridine (116 cm^3) under nitrogen at 0 °C. After 20 h at 0 °C, the mixture was poured onto crushed ice and extracted with ether (4 × 200 cm^3). The extract was washed with water, with 10% citric acid solution and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 20:80) to give the β-*lactone* (10.55 g, 95%); $[\alpha]_D^{21}$ −21.31 (*c* 2.06 in $CHCl_3$); R_f (EtOAc–hexane, 3:7) 0.34; ν_{max}(film)/cm^{-1} 1820 (C=O, β-lactone), 1730 (C=O), 1600 (Ar), 1260 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.40 (2 H, d, *J* 7.9, Ar), 7.21 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 7.12 (2 H, d, *J* 7.9, Ar), 4.17 (1 H, ddd, *J* 4.1, 4.1 and 8.2, CHOCO), 3.87–3.62 (4 H, m, OCH_2CH_2O), 3.55 (3 H, s, OMe), 3.43 (1 H, dd, *J* 4.1 and 7.4, CHCOO), 2.82 (1 H, dd, *J* 6.2 and 16.2, C$H_A$$H_B$$CO_2$Me), 2.52 (1 H, dd, *J* 8.5 and 16.2, $CH_AC$$H_B$-$CO_2$Me), 2.36 (3 H, s, 4-*Me*C_6H_4), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.15 (1 H, ddd, *J* 1.1, 6.2 and 8.5, SiCH), 1.97 (1 H, dd, *J* 8.2 and 14.6, CH_AH_BCHOCO), 1.77 (1 H, dd, *J* 1.1 and 7.4, SiCH), 1.71 (1 H, dd, *J* 1.5 and 14.6, C$H_A$$H_B$CHOCO), 1.1 (3 H, s, MeC), 0.32 (3 H, s, SiMe), 0.31 (3 H, s, SiMe), 0.28 (3 H, s, SiMe) and 0.21 (3 H, s, SiMe) (Found: C, 65.33; H, 8.10. $C_{31}H_{44}O_6Si_2$ requires C, 65.45; H, 7.80%), and the minor (5*S*,6*R*)-diastereoisomer of the aldol reaction (410 mg, 3%). Similarly, the (5*S*,6*S*)-diastereoisomer gave a β-lactone (95%).

Methyl (5*E*,3*S*,4*R*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-7-(2-methyldioxolan-2-yl)hept-5-enoate 15

Method A. The (5*R*,6*R*) β-lactone (9 g, 15.845 mmol) in collidine (50 cm^3) was stirred under nitrogen at 164 °C for 14 h. The solvent was removed by distillation under reduced pressure and the residue was chromatographed (SiO_2, EtOAc–hexane, 15:85) to give the allylsilanes (8.1 g, 98%) as a mixture of *E*- and *Z*-isomers. The isomers were separated by chromatography (SiO_2) to give pure *E*-isomer and a mixture of *E*- and *Z*-isomers. The mixed fraction was rechromatographed (SiO_2, $AgNO_3$, 70:30, EtOAc–hexane, 10:90) and the crops combined to give the E-*allylsilane* **15** (7.8 g, 94%); $[\alpha]_D^{21}$ +2.5 (*c* 2.24 in $CHCl_3$); R_f (Et_2O–hexane, 3:7) 0.6; ν_{max}($CDCl_3$)/cm^{-1} 1740 (C=O), 1600 (Ar), 1250 (SiMe), 1100 (SiAr) and 965 (*trans* CH=CH); δ_H(250 MHz; $CDCl_3$) 7.36 (2 H, d, *J* 7.8, Ar), 7.27

(2 H, d, *J* 7.8, Ar), 7.13 (2 H, d, *J* 7.8, Ar), 7.10 (2 H, d, *J* 7.8, Ar), 5.31–5.14 (2 H, m, CH=CH), 3.95–3.85 (4 H, m, OCH_2CH_2O), 3.44 (3 H, s, OMe), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.32 (3 H, s, 4-*Me*C_6H_4), 2.29–2.13 (4 H, m, C*H*$_2$CH=CH and C*H*$_2CO_2$Me), 2.03–1.96 (1 H, m, SiCH), 1.72 (1 H, q, *J* 6.9, SiCH), 1.26 (3 H, s, MeC), 0.24 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.19 (3 H, s, SiMe) and 0.18 (3 H, s, SiMe); *m*/*z* 524 (14.2%, M^+), 375 (10, M − 4-$MeC_6H_4SiMe_2$), 149 (100, 4-$MeC_6H_4SiMe_2$) and 87 (99, $C_4H_7O_2$) (Found: M^+, 524.2781. $C_{30}H_{44}O_4Si_2$ requires *M*, 524.2778) (Found: C, 68.47; H, 8.47. $C_{30}H_{44}O_4Si_2$ requires C, 68.65; H, 8.45%), and the Z-*allylsilane* (230 mg, 3%); R_f (Et_2O–hexane, 3:7) 0.57; ν_{max}(film)/cm^{-1} 1735 (C=O), 1635 (*cis* C=C), 1600 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.37 (2 H, d, *J* 7.8, Ar), 7.28 (2 H, d, *J* 7.8, Ar), 7.14 (2 H, d, *J* 7.8, Ar), 7.10 (2 H, d, *J* 7.8, Ar), 5.44–5.27 (2 H, m, CH=CH), 3.96–3.83 (4 H, m, OCH_2CH_2O), 3.47 (3 H, s, OMe), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.32 (3 H, s, 4-*Me*C_6H_4), 2.30–2.22 (4 H, m, CH_2CO_2Me and C*H*$_2$CH=CH), 1.98 (1 H, dd, *J* 6.3 and 10.5, SiCH), 1.73 (1 H, q, *J* 6.3, SiCH), 1.25 (3 H, s, MeC), 0.25 (3 H, s, SiMe), 0.20 (6 H, s, 2 × SiMe) and 0.17 (3 H, s, SiMe); *m*/*z* 524 (80.3%, M^+), 375 (70, M − 4-$MeC_6H_4SiMe_2$), 149 (92, 4-$MeC_6H_4SiMe_2$) and 87 (100, $C_4H_7O_2$) (Found: M^+, 524.2751. $C_{30}H_{44}O_4Si_2$ requires *M*, 524.2778). Similarly, the (5*S*,6*S*)-lactone gave the same (*E*)-allylsilane **15** (90%).

Method B. Following Mulzer,[30] the combined hydroxy acids (600 mg) derived from the (5*R*,6*S*) and (5*S*,6*R*) isomers of the aldol product **14** and *N*,*N*-dimethylformamide dineopentyl acetal (072 cm^3, 2.57 mmol) were stirred in chloroform (20 cm^3) at room temperature for 1 h, and the mixture was refluxed for 6 h. The mixture was poured into water and extracted with chloroform (2 × 10 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 20:80) to give the (E)-*allylsilane* (76%), identical with the earlier sample, and added to it for the next step.

Methyl (5*E*,3*RS*,4*SR*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-8-oxonon-5-enoate

The racemic version of the *E*-allylsilane **15** on standing in deuterochloroform solution gave the *ketone*; R_f (Et_2O–hexane, 2:8) 0.28; ν_{max}($CHCl_3$)/cm^{-1} 1725 (C=O), 1600 (Ar), 1260 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.32 (2 H, d, *J* 7.9, Ar), 7.29 (2 H, d, *J* 7.9, Ar), 7.13 (2 H, d, *J* 7.9, Ar), 7.10 (2 H, d, *J* 7.9, Ar), 5.30–5.12 (2 H, m, CH=CH), 3.45 (3 H, s, OMe), 2.97 (1 H, dd, *J* 5.3 and 16, C*H*$_A$H$_B$COMe), 2.88 (1 H, dd, *J* 5.9 and 16, CH$_A$*H*$_B$COMe), 2.29 (3 H, s, 4-*Me*C_6H_4), 2.28 (3 H, s, 4-*Me*C_6H_4), 2.27–2.13 (2 H, m, C*H*$_2CO_2$Me), 1.99 (3 H, s, *Me*$COCH_2$), 2.0–1.95 (1 H, m, SiCH), 1.69 (1 H, ddd, *J* 6.1, 6.1 and 8, SiCH), 0.22 (3 H, s, SiMe), 0.18 (3 H, s, SiMe), 0.12 (6 H, s, 2 × SiMe); *m*/*z* 480 (1.5%, M^+), 91 (80, 4-MeC_6H_4) and 43 (100, MeCO) (Found: M^+, 480.2560. $C_{28}H_{40}O_3Si_2$ requires *M*, 480.2516).

Methyl (5*Z*,3*RS*,4*SR*)-3,4-bis[dimethyl(4-methylphenyl)silyl]-8-oxonon-5-enoate

The racemic version of the corresponding *Z*-allylsilane on standing in deuterochloroform solution gave the *ketone*; R_f (Et_2O–hexane, 2:8) 0.24; ν_{max}($CHCl_3$)/cm^{-1} 1725 (C=O), 1600 (Ar), 1260 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.33 (2 H, d, *J* 7.9, Ar), 7.29 (2 H, d, *J* 7.9, Ar), 7.13 (2 H, d, *J* 7.9, Ar), 7.11 (2 H, d, *J* 7.9, Ar), 5.53–5.36 (2 H, m, CH=CH), 3.49 (3 H, s, OMe), 2.91 (1 H, dd, *J* 5.2 and 18, C*H*$_A$H$_B$COMe), 2.63 (1 H, dd, *J* 5.2 and 18, CH$_A$*H*$_B$COMe), 2.33 (1 H, dd, *J* 6.1 and 16.5, C*H*$_A$CH$_B$CO$_2$), 2.29 (6 H, s, 2 × 4-*Me*C_6H_4), 2.2 (1 H, dd, *J* 6.7 and 16.5, CH$_A$*H*$_B$CO$_2$Me), 2.19 (1 H, dd, *J* 6.7 and 11.1, SiCH), 1.98 (3 H, s, *Me*$COCH_2$), 1.73 (1 H, ddd, *J* 5.8, 6.7 and 6.7, SiCH), 0.25 (3 H, s, SiMe), 0.20 (6 H, s, 2 × SiMe) and 0.13 (3 H, s, SiMe); *m*/*z* 480 (17.3%, M^+), 149 (100, 4-$MeC_6H_4SiMe_2$) and 43 (35, MeCO) (Found: M^+, 480.2491. $C_{28}H_{40}O_3Si_2$ requires *M*, 480.2516).

(5*E*,3*S*,4*R*)-3,4-Bis[dimethyl(4-methylphenyl)silyl]-7-(2-methyldioxolan-2-yl)hept-5-enoic acid 16

Potassium hydroxide (10 mol dm^{-3} in H_2O, 28 cm^3) was added to the allylsilane **15** (5.89 g, 11.24 mmol) in THF (55 cm^3) and methanol (195 cm^3), and the mixture kept for 10 h at 45 °C. The solution was evaporated under reduced pressure and the residue was dissolved in water (100 cm^3), acidified with aqueous citric acid (10%) and extracted with ether (3 × 150 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *carboxylic acid* **16** (5.73 g, 100%); $[\alpha]_D^{20}$ +4.2 (*c* 2.46 in $CHCl_3$); R_f (EtOAc–hexane, 3:7) 0.18; ν_{max}($CHCl_3$)/cm^{-1} 3400–2500 (br, CO_2H), 1705 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.36 (2 H, d, *J* 7.8, Ar), 7.27 (2 H, d, *J* 7.8, Ar), 7.12 (2 H, d, *J* 7.8, Ar), 7.10 (2 H, d, *J* 7.8, Ar), 5.31–5.15 (2 H, m, CH=CH), 3.97–3.85 (4 H, m, OCH_2CH_2O), 2.39–2.16 (4 H, m, C*H*$_2CO_2$H and C*H*$_2$CH=CH), 2.31 (3 H, s, 4-*Me*C_6H_4), 2.30 (3 H, s, 4-*Me*C_6H_4), 2.03–1.95 (1 H, m, SiCH), 1.72 (1 H, q, *J* 6.5, SiCH), 1.26 (3 H, s, MeC), 0.24 (3 H, s, SiMe), 0.20 (6 H, s, 2 × SiMe) and 0.19 (3 H, s, SiMe); *m*/*z* 510 (9.6%, M^+), 509 (17.3, M − H), 149 (100, 4-$MeC_6H_4SiMe_2$) and 87 (90, $C_4H_7O_2$) (Found: M^+, 510.2571. $C_{29}H_{42}O_4Si_2$ requires *M*, 510.2621). The enantiomeric purity was checked at this stage by derivatising with (*R*)-(+)-phenyl ethyl alcohol. The ratio of diastereoisomers was 96:4 (^{1}H NMR), confirming that no loss of enantiomeric purity had occurred.

(3*S*,4*S*,5*S*,6*S*)-3,5-Bis[dimethyl(4-methylphenyl)silyl]-6-hydroxy-7-(2-methyldioxolan-2-yl)heptano-4-lactone 17

The carboxylic acid **16** (6.4 g, 12.55 mmol), 3-chloroperoxybenzoic acid (50% w/w, 10.5 g, 30.5 mmol) and anhydrous disodium hydrogen orthophosphate (40 g, 282 mmol) were stirred in dichloromethane (250 cm^3) for 4 h at 0 °C. The mixture was allowed to come slowly to room temperature and stirred for a further 8 h. The mixture was filtered and the filtrate was diluted with ether (300 cm^3), washed with aqueous sodium thiosulfate, with aqueous sodium hydrogen carbonate and with brine, dried (K_2CO_3) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 3:7) to give the *lactone* (6.04 g, 92%); $[\alpha]_D^{20}$ +35.95 (*c* 4.8 in $CHCl_3$); R_f (EtOAc–hexane, 3:7) 0.31; ν_{max}($CHCl_3$)/cm^{-1} 3500 (OH), 1770 (C=O), 1600 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.33 (2 H, d, *J* 7.9, Ar), 7.29 (2 H, d, *J* 7.9, Ar), 7.18 (2 H, d, *J* 7.9, Ar), 7.15 (2 H, d, *J* 7.9, Ar), 4.96 (1 H, d, *J* 11.3, CHOCO), 4.07–3.99 (1 H, m, C*H*OH), 3.98–3.86 (4 H, m, OCH_2CH_2O), 3.48 (1 H, br s, OH), 2.36 (3 H, s, 4-*Me*C_6H_4), 2.34 (3 H, s, 4-*Me*C_6H_4), 2.15 (1 H, dd, *J* 12.7 and 17.4, C*H*$_A$H$_B$COO), 2.04 (1 H, dd, *J* 9.2 and 17.4, CH$_A$*H*$_B$COO), 1.65–1.56 (3 H, m, C*H*$_2$CHOH and SiCH), 1.47 (1 H, ddd, *J* 9.2, 11.3 and 12.7, SiCH), 1.19 (3 H, s, MeC), 0.40 (3 H, s, SiMe), 0.37 (3 H, s, SiMe), 0.29 (3 H, s, SiMe) and 0.26 (3 H, s, SiMe); δ_C(100 MHz; $CDCl_3$) 177.4, 139.7, 138.9, 135.5, 134.2, 134.0, 132.2, 128.9, 128.7, 110.1, 83.8, 66.2, 64.6, 64.2, 44.8, 40.4, 31.7, 29.1, 23.9, 21.5, 21.4, −0.8, −1.2, −4.2, −4.6; *m*/*z* 526 (0.5%, M^+), 511 (2.5, M − Me), 509 (1.5, M − OH), 149 (100, 4-$MeC_6H_4SiMe_2$) and 87 (100, $C_4H_7O_2$) (Found: C, 65.99; H, 7.77; M^+, 526.2534. $C_{29}H_{42}O_5Si_2$ requires C, 66.11; H, 8.04%; *M*, 526.2571), and a minor diastereoisomer, presumably the (5*R*,6*R*) *lactone* (200 mg, 3%); R_f (EtOAc–hexane, 3:7) 0.36; ν_{max}($CHCl_3$)/cm^{-1} 3500 (OH), 1760 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.36 (2 H, d, *J* 7.8, Ar), 7.18 (4 H, d, *J* 7.8, Ar), 7.09 (2 H, d, *J* 7.8, Ar), 4.85 (1 H, dd, *J* 1.5 and 8.7, CHOCO), 4.06 (1 H, dd, *J* 5.5 and 10.1, C*H*OH), 3.99–3.80 (4 H, m, OCH_2CH_2O), 3.27 (1 H, br s, OH), 2.76 (1 H, dd, *J* 13 and 16.9, C*H*$_A$H$_B$COO), 2.42–2.16 (2 H, m, CH$_A$*H*$_B$COO and SiCH), 2.39 (3 H, s, 4-*Me*C_6H_4), 2.35 (3 H, s, 4-*Me*C_6H_4), 1.90 (1 H, d, *J* 14.6, C*H*$_A$H$_B$CHOH), 1.69 (1 H, dd, *J* 10.1 and 14.6, CH$_A$*H*$_B$CHOH), 1.36 (1 H, dd, *J* 1.5 and 5.5, SiCH), 1.17 (3 H, s, MeC), 0.39 (3 H, s, SiMe), 0.31 (3 H, s, SiMe) and 0.30 (6 H, s, 2 × SiMe); *m*/*z* 526 (0.01%, M^+), 511

(0.4, M − Me), 149 (45, 4-$MeC_6H_4SiMe_2$) and 87 (100, $C_4H_7O_2$) (Found: M^+, 526.2578. $C_{29}H_{42}O_5Si_2$ requires *M*, 526.2571).

(4*E*,3*RS*,6*RS*)-3-[Dimethyl(4-methylphenyl)silyl]-6-[dimethyl(4-methylphenyl)silyl]oxy-7-(2-methyldioxolan-2-yl)hept-4-enoic acid

The racemic hydroxy lactone corresponding to **17** (700 mg, 1.33 mmol) in dry THF (10 cm^3) was added to a stirred suspension of potassium hydride (20% w/w suspension in oil, prewashed with dry hexane, 1 g, 5 mmol) in dry THF (35 cm^3) under argon at −78 °C. The temperature was raised to −20 °C over 2 h, then to −5 °C over 1 h and then stirred at 0 °C for 1 h. Aqueous ammonium chloride was added carefully at −78 °C, the mixture acidified with aqueous citric acid (10%) and extracted with ether (3 × 50 cm^3). The extracts were washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the acid (670 mg, 96%). This was characterised as its *methyl ester* by treating it with ethereal diazomethane; R_f (EtOAc–hexane, 3:7) 0.51; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O), 1600 (Ar), 1250 (SiMe), 1105 (SiAr) and 970 (*trans* CH=CH); δ_H(250 MHz; $CDCl_3$) 7.45 (2 H, d, *J* 7.9, Ar), 7.34 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 7.15 (2 H, d, *J* 7.9, Ar), 5.44 (1 H, dd, 6.5 and 15.6, SiCHC*H*=CH), 5.33 (1 H, dd, 6 and 15.6, CH=C*H*CHOSi), 4.25 (1 H, q, *J* 6, CHOSi), 3.90–3.73 (4 H, m, OCH_2CH_2O), 3.53 (3 H, s, OMe), 2.33 (6 H, s, 2 × 4-*Me*C_6H_4), 2.33–2.18 (3 H, m, CH_2CO_2Me and SiCH), 1.87 (1 H, dd, *J* 6.3 and 14.3, CH_AH_BCHOH), 1.70 (1 H, dd, *J* 5.7 and 14.3, CH_AH_BCHOH), 1.26 (3 H, s, MeC), 0.32 (3 H, s, SiMe), 0.31 (3 H, s, SiMe), 0.23 (3 H, s, SiMe) and 0.22 (3 H, s, SiMe); δ_C(100 MHz, $CDCl_3$) 173.69, 139.26, 139.14, 134.60, 134.02, 133.68, 132.97, 132.48, 129.25, 128.64, 128.48, 108.87, 70.73, 64.23, 64.15, 51.43, 47.33, 33.90, 28.17, 24.56, 21.50, 21.45, −0.80, −1.06, −4.32 and −5.35 (Found: C, 66.70; H, 8.24. $C_{30}H_{44}O_5Si_2$ requires C, 66.62; H, 8.20%).

(3*R*,6*R*)-3-[Dimethyl(4-methylphenyl)silyl]-6-hydroxy-7-(2-methyldioxolan-2-yl)heptanoic acid 19

The hydroxy lactone **17** (5.8 g, 11.027 mmol) in dry THF (100 cm^3) was added to a stirred suspension of potassium hydride (20% w/w suspension in oil, prewashed with dry hexane, 6.5 g, 32.5 mmol) in dry THF (200 cm^3) under argon at −78 °C. The temperature was raised to −20 °C over 2 h, then to −5 °C over 1 h and then stirred at 0 °C for 2 h. Aqueous ammonium chloride was added carefully into it at −78 °C, acidified with aqueous citric acid (10%) and extracted with ether (3 × 150 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue in methanol (600 cm^3) was stirred with platinum oxide (200 mg) under hydrogen for 50 h at room temperature and the mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and chromatographed (SiO_2, EtOAc–hexane, 8:2) to give the *hydroxy acid* (3.64 g, 87%); $[a]_D^{23}$ −1.94 (*c* 1.91 in $CHCl_3$); R_f (EtOAc) 0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (br, OH), 3500–2500 (br, COOH), 1700 (C=O), 1600 (Ar), 1260 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.8, Ar), 7.15 (2 H, d, *J* 7.8, Ar), 3.99–3.93 (4 H, m, OCH_2CH_2O), 3.84–3.72 (1 H, m, C*H*OH), 2.38 (1 H, dd, *J* 4.8 and 16, C$H_AH_BCO_2H$), 2.32 (3 H, s, 4-*Me*C_6H_4), 2.22 (1 H, dd, *J* 8.3 and 16, $CH_AH_BCO_2H$), 1.74–1.61 (3 H, m, CH_2 and SiCH), 1.47–1.130 (4 H, m, 2 × CH_2), 1.31 (3 H, s, MeC), 0.28 (3 H, s, Si*Me*$_A$Me$_B$) and 0.27 (3 H, s, SiMe$_A$*Me*$_B$). This acid was further characterised as its methyl ester, with data given below in the sequence describing the synthesis of benzyl (−)-nonactate **25**.

(3*R*,6*R*)-3-[Dimethyl(4-methylphenyl)silyl]-6-hydroxy-8-oxo-nonanoic acid

The hydroxy acid **19** (3.45 g, 9.08 mmol) and pyridinium toluene-*p*-sulfonate (750 mg, 3 mmol) were refluxed in acetone (125 cm^3) and water (2.5 cm^3) for 7 h. The solvent was removed under reduced pressure and the residue was taken up in ether (250 cm^3). The ether was washed with aqueous citric acid and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *ketone* (3.0 g, 98%); R_f (EtOAc–hexane–AcOH, 49:50:1) 0.15; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 3500–2500 (br, COOH), 1710 (C=O), 1600 (Ar), 1260 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.8, Ar), 7.16 (2 H, d, *J* 7.8, Ar), 4.0–3.87 (1 H, m, C*H*OH), 2.43 (2 H, d, *J* 6.0, CH_2COMe), 2.38 (1 H, dd, *J* 4.5 and 16, C$H_AH_BCO_2H$), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.21 (1 H, dd, *J* 9 and 16, $CH_AH_BCO_2H$), 2.12 (3 H, s, MeCO), 1.70–1.57 (1 H, m, CH_AH_B), 1.45–1.20 (4 H, m, CH_2, CH_AH_B and SiCH), 0.29 (3 H, s, Si*Me*$_A$Me$_B$) and 0.28 (3 H, s, SiMe$_A$*Me*$_B$); further characterised as its *methyl ester* by treatment with diazomethane; $[a]_D^{22}$ −18.82 (*c* 2.12 in $CHCl_3$); R_f (EtOAc–hexane, 2:8) 0.14; $\nu_{max}(CHCl_3)/cm^{-1}$ 3700–3400 (br, OH), 1730 (C=O), 1715 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 3.97–3.87 (1 H, m, C*H*OH), 3.58 (3 H, s, OMe), 3.02 (1 H, d, *J* 3.5, OH, D_2O exchangeable), 2.42 (2 H, d, *J* 6.0, CH_2COMe), 2.35 (1 H, dd, *J* 5.5 and 16, C$H_AH_BCO_2Me$), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.19 (1 H, dd, *J* 8.8 and 16, $CH_AH_BCO_2Me$), 2.12 (3 H, s, MeCO), 1.67–1.55 (1 H, m, CH_AH_B), 1.41–1.19 (4 H, m, CH_2, CH_AH_B and SiCH), 0.27 (3 H, s, Si*Me*$_A$Me$_B$) and 0.26 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 335 (4.1%, M − Me), 259 (63, M − 4-MeC_6H_4), 149 (100, 4-$MeC_6H_4SiMe_2$) and 91 (53, MeC_6H_4) (Found: C, 65.24; H, 8.54. $C_{19}H_{30}O_4Si$ requires C, 65.10; H, 8.63%).

(3*R*,6*R*,8*R*)-6,8-Dihydroxy-3-[dimethyl(4-methylphenyl)silyl]-nonanoic acid

The ketone (2.95 g, 8.779 mmol) in acetonitrile (28 cm^3) was added to a stirred solution of tetramethylammonium triacetoxyborohydride[16] (16.7 g, 63.5 mmol) in acetonitrile and acetic acid (45 cm^3) under argon at −30 °C, and the mixture was stirred at −25 °C for 48 h. Acetonitrile (25 cm^3) and glycerol (25 cm^3) were added to the mixture, stirred at room temperature over 15 min and evaporated under reduced pressure. The residue was diluted with water and extracted with chloroform (5 × 100 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane–AcOH, 80:20:1) to give the anti-*diol* (2.65 g, 89%); $[a]_D^{21}$ −7.0 (*c* 1.53 in $CHCl_3$); R_f (EtOAc–hexane–AcOH, 80:20:1) 0.10; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 3500–2500 (br, COOH), 1710 (C=O), 1600 (Ar), 1260 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.90 Ar), 5.37 (2 H, br, 2 × OH), 4.12–3.98 (1 H, m, C*H*OH), 3.94–3.80 (1 H, m, C*H*OH), 2.40 (1 H, dd, *J* 3.3 and 16, C$H_AH_BCO_2H$), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.16 (1 H, dd, *J* 10.1 and 16, $CH_AH_BCO_2H$), 1.65–1.33 (7 H, m, 3 × CH_2 and SiCH), 1.16 (3 H, d, *J* 6.3, *Me*CHOH), 0.28 (3 H, s, Si*Me*$_A$Me$_B$) and 0.27 (3 H, s, SiMe$_A$*Me*$_B$), and the *syn*-diol (120 mg, 4%). The major diastereoisomer was further characterised as its *methyl ester* by treatment with diazomethane; R_f (EtOAc–hexane–AcOH, 50:50:1) 0.22; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (br, OH), 1740 (C=O), 1600 (Ar), 1250 (SiMe) and 1110 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.37 (2 H, d, *J* 7.8, Ar), 7.16 (2 H, d, *J* 7.8, Ar), 4.12–3.99 (1 H, m, C*H*OH), 3.92–3.82 (1 H, m, C*H*OH), 3.59 (3 H, s, OMe), 2.76 (2 H, br s, OH), 2.37 (1 H, dd, *J* 4.4 and 16.1, C$H_AH_BCO_2Me$), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.19 (1 H, dd, *J* 9.4 and 16.1, $CH_AH_BCO_2Me$), 1.65–1.52 (1 H, m, SiCH), 1.49–1.21 (6 H, m, 3 × CH_2), 1.18 (3 H, d, *J* 6.3, *Me*CHOH), 0.28 (3 H, s, Si*Me*$_A$Me$_B$) and 0.27 (3 H, s, SiMe$_A$*Me*$_B$) (Found: C, 64.82; H, 8.98. $C_{19}H_{32}O_4Si$ requires C, 64.73; H, 9.15%).

(3*R*,6*R*,8*R*)-3-[Dimethyl(4-methylphenyl)silyl]-8-hydroxy nonano-6-lactone 20

The diol (600 mg, 1.775 mmol) and triethylamine (2.15 cm^3, 15.4 mmol) in dichloromethane (300 cm^3) were added dropwise with stirring to 2-chloro-1-methylpyridinium iodide[17] (2 g,

7.82 mmol) in dichloromethane (300 cm^3) under nitrogen under reflux over 9 h. After a further 1 h under reflux, the solution was washed with water, with aqueous citric acid, with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 4:6) to give the lactone (552 mg, 97%); needles of the racemate (19.5 mg, 3.4%), mp 100–101 °C (from hexane), were deposited from hexane, enhancing the ratio of enantiomers to 99.5:0.5 and giving the *lactone* (531.5 mg, 93.5%); $[\alpha]_D^{20}$ −27.14 (*c* 1.35 in $CHCl_3$); R_f (EtOAc–hexane, 4:6) 0.17; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (br, OH), 1720 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.17 (2 H, d, *J* 7.9, Ar), 4.70–4.65 (1 H, m, CHOCO), 4.08–3.98 (1 H, m, C*H*OH), 2.97 (1 H, dd, *J* 8.1 and 14.7, $CH_AH_BCO_2$), 2.61 (1 H, dd, *J* 5.3 and 14.7, $CH_AH_BCO_2$), 2.34 (3 H, s, 4-*Me*C_6H_4), 2.10 (1 H, br s, OH), 1.83–1.61 (5 H, m, 2 × CH_2 and CH_AH_BCHOH), 1.50 (1 H, ddd, *J* 2.4, 10 and 14.5, CH_AH_BCHOH), 1.30–1.21 (1 H, m, SiCH), 1.18 (3 H, d, *J* 6.3, *Me*CHOH), 0.33 (3 H, s, $SiMe_AMe_B$) and 0.32 (3 H, s, $SiMe_AMe_B$); *m/z* 275 (5.9%, M-MeCHOH) and 149 (100, 4-$MeC_6H_4SiMe_2$) (Found: C, 67.60; H, 8.82. $C_{18}H_{28}O_3Si$ requires C, 67.46; H, 8.81%).

(3*R*,6*R*,8*R*)-8-*tert*-Butyldimethylsilyloxy-3-[dimethyl(4-methylphenyl)silyl]nonano-6-lactone

The alcohol **20** (1.7 g, 5.315 mmol), *tert*-butyldimethylsilyl chloride (2.6 g, 17.25 mmol) and imidazole (2.5 g, 34.7 mmol) were stirred in dimethylformamide (20 cm^3) at room temperature for 15 h. The mixture was poured into water and extracted with ether (3 × 100 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 5:95) to give the *silyl ether* (2.2 g, 95%); $[\alpha]_D^{22}$ −61.9 (*c* 1.98 in Et_2O); R_f (EtOAc–hexane, 1:9) 0.44; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O), 1600 (Ar), 1250 (SiMe), 1100 (SiAr) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 7.40 (2 H, d, *J* 7.9, Ar), 7.18 (2 H, d, *J* 7.9, Ar), 4.58–4.48 (1 H, m, CHOCO), 4.09–3.96 (1 H, m, CHOSi), 2.86 (1 H, dd, *J* 7.5 and 14.4, $CH_AH_BCO_2$), 2.63 (1 H, dd, *J* 5.3 and 14.4, $CH_AH_BCO_2$), 2.34 (3 H, s, 4-*Me*C_6H_4), 1.78–1.64 (5 H, m, 2 × CH_2 and CH_AH_BCHOSi), 1.47 (1 H, ddd, *J* 2.2, 10.1 and 15.4 CH_AH_BCHOSi), 1.35–1.27 (1 H, m, SiCH), 1.11 (3 H, d, *J* 6.1, *Me*CHOSi), 0.87 (9 H, s, SiBu^t), 0.33 (3 H, s, $SiMe_AMe_B$), 0.32 (3 H, s, $SiMe_AMe_B$), 0.04 (3 H, s, $OSiMe_AMe_B$) and −0.01 (3 H, s, $OSiMe_AMe_B$) (Found: C, 66.49; H, 9.80. $C_{24}H_{42}O_3Si_2$ requires C, 66.30; H, 9.74%).

(2*R*,3*R*,6*R*,8*R*)-8-*tert*-Butyldimethylsilyloxy-3-[dimethyl(4-methylphenyl)silyl]-2-methylnonano-6-lactone 21

n-Butyllithium (1.45 mol dm^{-3} in hexane, 5 cm^3) was added dropwise to diisopropylamine (1.12 cm^3, 8 mmol) in dry THF (15 cm^3) under argon at −78 °C. After 20 min at 0 °C, the mixture was brought to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (10 cm^3) was added followed by the lactone (2.2g, 5.069 mmol) in dry THF (20 cm^3) over 10 min. The mixture was stirred for 1 h and methyl iodide (3 cm^3, 48 mmol) was added. After 36 h at −78 °C, the mixture was brought to −10 °C over 8 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ether (3 × 150 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 5:95) to give the *lactone* (2.2 g, 97%); $[\alpha]_D^{20}$ −17.76 (*c* 1.34 in $CHCl_3$); R_f (EtOAc–hexane, 1:9) 0.33; $\nu_{max}(CHCl_3)/cm^{-1}$ 1705 (C=O), 1600 (Ar), 1250 (SiMe), 1105 (SiAr) and 830 (OSi); δ_H(250 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 7.9, Ar), 7.17 (2 H, d, *J* 7.9, Ar), 4.78 (1 H, tt, *J* 3 and 10.8, C*H*OCO), 4.05 (1 H, ddq, *J* 3, 9 and 6.1, CHOSi), 3.06 (1 H, quintet, *J* 7.5, MeC*H*CO_2), 2.34 (3 H, s, 4-*Me*C_6H_4), 1.87–1.34 (6 H, m, 3 × CH_2), 1.23 (3 H, d, *J* 7.5, *Me*CHCO_2), 1.13 (3 H, d, *J* 6.1, *Me*CHOSi), 0.87 (9 H, s, SiBu^t), 0.78 (1 H, dt, *J* 1.3, 7.8, SiCH), 0.31 (3 H, s, $SiMe_AMe_B$), 0.30 (3 H, s, $SiMe_AMe_B$), 0.05 (3 H, s, $OSiMe_AMe_B$) and 0.02 (3 H, s, $OSiMe_AMe_B$); *m/z* 449 (0.6%, M + H), 448 (0.2, M^+), 391 (30, M − Bu^t), 149 (100, 4-$MeC_6H_4SiMe_2$) and 75 (50, $SiMe_2OH$) (Found: C, 67.06; H, 9.77. $C_{25}H_{44}O_3Si_2$ requires C, 66.91; H, 9.88%).

(2*S*,3*R*,6*R*,8*R*)-8-*tert*-Butyldimethylsilyloxy-3-hydroxy-2-methylnonano-6-lactone

Peracetic acid (32% w/v solution in acetic acid, 40 cm^3) was added dropwise to a stirred suspension of the lactone **21** (1.7 g, 3.794 mmol), potassium bromide (680 mg, 5.71 mmol) and sodium acetate (15 g, 183 mmol) in acetic acid (40 cm^3) at 0 °C, and the mixture stirred for 15 h at room temperature. The solvent was azeotropically evaporated with toluene under reduced pressure at room temperature. The residue was taken up in ethyl acetate and washed with aqueous sodium thiosulfate, with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 4:6) to give the *lactone* (870 mg, 73%); mp 63–64 °C (the crystals were freely soluble in common organic solvents, and could not be recrystallised); $[\alpha]_D^{21}$ −101.63 (*c* 1.23 in $CHCl_3$); R_f (EtOAc–hexane, 4:6) 0.17; $\nu_{max}(CHCl_3)/cm^{-1}$ 3700 (br, OH), 1710 (C=O) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 4.63 (1 H, dt, *J* 2.2 and 10.2, C*H*OCO), 4.09 (1 H, ddq, *J* 2.1, 8.2 and 6.1, CHOSi), 3.94–3.88 (1 H, m, C*H*OH), 3.14 (1 H, dq, *J* 5.4 and 7.6, MeC*H*CO_2), 2.19–1.88 (4 H, m, CH_2, CH_AH_B and OH), 1.75 (1 H, ddd, *J* 2.4, 10.1 and 14.2, CH_AH_BCHOSi), 1.70–1.59 (1 H, m, CH_AH_B), 1.50 (1 H, ddd, *J* 2.1, 10.2 and 14.2, CH_AH_BCHOSi), 1.34 (3 H, d, *J* 7.6, *Me*CHCO_2), 1.12 (3 H, d, *J* 6.1, *Me*CHOSi), 0.87 (9 H, s, SiBu^t), 0.05 (3 H, s, $SiMe_AMe_B$) and 0.02 (3 H, s, $SiMe_AMe_B$) (Found: C, 60.88; H, 10.25. $C_{16}H_{32}O_4Si$ requires C, 60.72; H, 10.19%). In the racemic series, the lactone was obtained as plates, mp 96–97 °C (from hexane).

(2*S*,3*R*,6*R*,8*R*)-8-*tert*-Butyldimethylsilyloxy-2-methyl-3-(4-methylphenyl)sulfonyloxynonano-6-lactone

The alcohol (950 mg, 3 mmol), toluene-*p*-sulfonyl chloride (3 g, 15.7 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) were kept in anhydrous pyridine (10 cm^3) at room temperature for 5 days. Crushed ice was added, the mixture stirred for 15 min and extracted with dichloromethane (3 × 50 cm^3). The extract was washed with aqueous citric acid and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 2:8) to give the *tosylate* (1.35 g, 96%); $[\alpha]_D^{21}$ −83.0 (*c* 1.79 in $CHCl_3$); R_f (EtOAc–hexane, 4:6) 0.63; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O), 1180 (OSO_2) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.3, Ar), 7.33 (2 H, d, *J* 8.3, Ar), 4.68 (1 H, t, *J* 5.1, CHOTs), 4.54 (1 H, br t, *J* 8.3, CHOCO), 4.05 (1 H, ddq, *J* 2, 10.1 and 6.1, CHOSi), 3.17 (1 H, dq, *J* 5.9 and 7.3, MeC*H*CO), 2.43 (3 H, s, 4-*Me*C_6H_4), 2.17–1.95 (3 H, m, CH_2 and CH_AH_B), 1.78–1.67 (2 H, m, CH_AH_BCHOSi and CH_AH_B), 1.47 (1 H, ddd, *J* 2.0, 10.1 and 14, CH_AH_BCHOSi), 1.18 (3 H, d, *J* 7.6, *Me*CHCO_2), 1.10 (3 H, d, *J* 6.1, *Me*CHOSi), 0.84 (9 H, s, SiBu^t), 0.03 (3 H, s, $SiMe_AMe_B$) and −0.02 (3 H, s, $SiMe_AMe_B$) (Found: C, 58.64; H, 8.26. $C_{23}H_{38}O_6SiS$ requires C, 58.69; H, 8.14%). In the racemic series, the tosylate was obtained as needles; mp 125–126 °C (from hexane).

Methyl (+)-nonactate 4

The tosylate (1.325 g, 2.82 mmol) and toluene-*p*-sulfonic acid (500 mg, 2.63 mmol) were kept in dry methanol (25 cm^3) at room temperature for 4 days. The mixture was evaporated under reduced pressure and the residue was taken up in ether (50 cm^3). The ether was washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 4:6) to give (+)-methyl nonactate (580 mg, 95%); $[\alpha]_D^{22}$ +22.55 (*c* 1.14 in $CHCl_3$) {lit.,[31] $[\alpha]_D^{25}$ +22.1 (*c* 0.7 in

$CHCl_3$)}; R_f (EtOAc–hexane, 4:6) 0.24; ν_{max}(film)/cm^{-1} 3600–3200 (br, OH) and 1730 (C=O); δ_H(400 MHz; $CDCl_3$) 4.15–4.09 (1 H, m, CHO), 4.05–3.93 (2 H, m, CHO and C*H*OH), 3.68 (3 H, s, OMe), 2.89 (1 H, br s, OH), 2.52 (1 H, dq, *J* 8.2 and 7.0, MeC*H*CO_2Me), 2.02–1.92 (2 H, m, CH_2), 1.76–1.57 (4 H, m, 2 × CH_2), 1.19 (3 H, d, *J* 6.3, *Me*CHOH), 1.11 (3 H, d, *J* 7.0, *Me*CHCO_2Me); δ_C(100 MHz, $CDCl_3$) 175.25, 81.07, 77.34, 65.17, 51.70, 45.30, 42.69, 30.54, 28.83, 23.19, 13.53 matching the NMR spectra reported by Bartlett.[26] The enantiomeric purity was measured by GC on a chiral capillary column [β-cyclodextrin (CYDEX-B), 25 m, film thickness 25 micron, helium carrier; 120 °C, 5 min; 1 °C min^{-1} up to 150 °C; 150 °C isothermal; t_R for methyl (−)-nonactate, 38.49 min and t_R for methyl (+)-nonactate, 38.95 min]: the peaks were in a ratio of 0.38:99.62.

Methyl (3*R*,6*R*)-3-[dimethyl(4-methylphenyl)silyl]-6-hydroxy-7-(2-methyldioxolan-2-yl)heptanoate

The hydroxy lactone **17** (5.8 g, 11.027 mmol) was converted into the acid **19**, as described above. The crude acid was esterified with ethereal diazomethane and chromatographed (SiO_2, EtOAc–hexane, 8:2) to give the *methyl ester* (3.47 g, 80%); $[\alpha]_D^{23}$ −2.72 (*c* 1.92 in $CHCl_3$); R_f (EtOAc–hexane, 2:8) 0.15; ν_{max}($CHCl_3$)/cm^{-1} 3700–3400 (br, OH), 1725 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.15 (2 H, d, *J* 7.9, Ar), 4.00–3.93 (4 H, m, OCH_2-CH_2O), 3.85–3.71 (1 H, m, C*H*OH), 3.56 (3 H, s, OMe), 3.54 (1 H, br s, OH, D_2O exchangeable), 2.35 (1 H, dd, *J* 5.4 and 15.7, CH_AH$_B$$CO_2$Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.21 (1 H, dd, *J* 8.2 and 15.7, CH$_A$$H_B$$CO_2$Me), 1.74–1.56 (3 H, m, CH_2 and SiCH), 1.43–1.16 (4 H, m, 2 × CH_2), 1.32 (3 H, s, MeC), 0.27 (3 H, s, SiMe_AMe$_B$) and 0.26 (3 H, s, SiMe$_A$$Me_B$) (Found: C, 64.02; H, 8.73. $C_{21}H_{34}O_5Si$ requires C, 63.92; H, 8.69%).

(3*R*,6*R*)-Methyl 3-[dimethyl(4-methylphenyl)silyl]-6-hydroxy-8-oxononanoate

The hydroxy ester (3.3 g, 8.376 mmol) and pyridinium toluene-*p*-sulfonate (750 mg, 3 mmol) were refluxed in acetone (125 cm^3) and water (2.5 cm^3) for 2.5 h. The solvent was evaporated under reduced pressure and the residue was taken up in ether (150 cm^3). The ether was washed with aqueous sodium hydrogen carbonate, with aqueous citric acid and with brine, dried ($MgSO_4$) and evaporated to give the *ketone* (2.72 g, 93%); $[\alpha]_D^{22}$ −18.82 (*c* 2.12 in $CHCl_3$); R_f (EtOAc–hexane, 2:8) 0.14; ν_{max}($CHCl_3$)/cm^{-1} 3700–3400 (br, OH), 1730 (C=O), 1715 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 3.97–3.87 (1 H, m, C*H*OH), 3.58 (3 H, s, OMe), 3.02 (1 H, d, *J* 3.5, OH, D_2O exchangeable), 2.42 (2 H, d, *J* 6.0, CH_2COMe), 2.35 (1 H, dd, *J* 5.5 and 16, CH_AH$_B$$CO_2$Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.19 (1 H, dd, *J* 8.8 and 16, CH$_A$$H_B$$CO_2$Me), 2.12 (3 H, s, MeCO), 1.67–1.55 (1 H, m, CH_AH$_B$), 1.41–1.19 (4 H, m, CH_2, CH$_A$$H_B$ and SiCH), 0.27 (3 H, s, SiMe_AMe$_B$) and 0.26 (3 H, s, SiMe$_A$$Me_B$); *m*/*z* 335 (4.1%, M − Me), 259 (63, M − 4-MeC_6H_4), 149 (100, 4-MeC_6H_4SiMe$_2$) and 91 (53, 4-MeC_6H_4) (Found: C, 65.24; H, 8.54. $C_{19}H_{30}O_4Si$ requires C, 65.10; H, 8.63%).

Methyl (3*R*,6*R*,8*S*)-6,8-dihydroxy-3-[dimethyl(4-methylphenyl)silyl]nonanoate

Following Prasad,[21] dibutylmethoxyborane (1.68 cm^3, 10 mmol) was added dropwise with stirring to the ketone (2.62 g, 7.48 mmol) in THF (10 cm^3) and methanol (2.5 cm^3) under argon at −78 °C. After 20 min at −78 °C, sodium borohydride (425 mg, 12 mmol) was added and the mixture was stirred for 15 h. Acetic acid (10.5 cm^3) was added dropwise at −78 °C and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 cm^3) and washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. To remove boron complexation, the residue was dissolved in methanol (50 cm^3) and the solvent was distilled off from a water bath. The residue was chromatographed (SiO_2, EtOAc–hexane–AcOH, 39:60:1) to give the syn-*diol* (2.2 g, 83%); $[\alpha]_D^{21}$ +3.9 (*c* 2.13 in $CHCl_3$); R_f (EtOAc–hexane–AcOH, 39:60:1) 0.30; ν_{max}($CHCl_3$)/cm^{-1} 3550–3200 (br, OH), 1720 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.37 (2 H, d, *J* 7.9, Ar), 7.17 (2 H, d, *J* 7.9, Ar), 4.04–3.89 (1 H, m, C*H*OH), 3.86–3.72 (1 H, m, C*H*OH) 3.61 (3 H, s, OMe), 3.49 (1 H, br s, OH), 3.29 (1 H, br s, OH), 2.38 (1 H, dd, *J* 4 and 16.4, CH_AH$_B$$CO_2$Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.18 (1 H, dd, *J* 9.7 and 16.4, CH$_A$$H_B$-$CO_2$Me), 1.61–1.24 (7 H, m, 3 × CH_2 and SiCH), 1.14 (3 H, d, *J* 6.3, *Me*CHOH), 0.28 (3 H, s, SiMe_AMe$_B$) and 0.27 (3 H, s, Si$Me_A$$Me_B$) (Found: C, 64.57; H, 9.03. $C_{19}H_{32}O_4Si$ requires C, 64.73; H, 9.15%), and the anti-*diol* (241 mg, 9%); $[\alpha]_D^{21}$ −7.4 (*c* 2.08 in $CHCl_3$); identical (^{1}H NMR) with the sample described above.

Acetonide of methyl (3*R*,6*R*,8*S*)-6,8-dihydroxy-3-[dimethyl-(4-methylphenyl)silyl]nonanoate 22

Pyridinium toluene-*p*-sulfonate (500 mg, 2 mmol) was stirred with the diol (1.8 g, 5.113 mmol) in 2,2-dimethoxypropane (18 cm^3) at room temperature for 15 h. The mixture was poured into aqueous sodium hydrogen carbonate and extracted with ether (3 × 100 cm^3). The extract was washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 10:90) to give the *acetonide* (1.93 g, 96%); $[\alpha]_D^{20}$ −7.1 (*c* 1.82 in $CHCl_3$); R_f (EtOAc–hexane 15:85) 0.30; ν_{max}(film)/cm^{-1} 1735 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 3.92–3.84 (1 H, m, CHO), 3.68–3.58 (1 H, m, CHO), 3.57 (3 H, s, OMe), 2.35 (1 H, dd, *J* 5.6 and 15.6, CH_AH$_B$$CO_2$Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 2.21 (1 H, dd, *J* 8.1 and 15.6, CH$_A$$H_B$$CO_2$Me), 1.61–1.17 (6 H, m, 3 × CH_2), 1.39 (3 H, s, *Me*$_A$Me$_B$C), 1.37 (3 H, s, Me$_A$*Me*$_B$C), 1.11 (3 H, d, *J* 6.1, *Me*CHO), 1.10–0.90 (1 H, m, SiCH), 0.27 (3 H, s, SiMe_AMe$_B$) and 0.26 (3 H, s, SiMe$_A$$Me_B$) (Found: C, 67.35; H, 9.21. $C_{22}H_{36}O_4Si$ requires C, 67.30; H, 9.24%).

Acetonide of methyl (2*S*,3*R*,6*R*,8*S*)-6,8-dihydroxy-3-[dimethyl-(4-methylphenyl)silyl]-2-methylnonanoate 23

n-Butyllithium (1.45 mol dm^{-3} in hexane, 5 cm^3) was added dropwise with stirring to diisopropylamine (1.12 cm^3, 8 mmol) in dry THF (20 cm^3) under argon at −78 °C. After 20 min at 0 °C, the mixture was brought to −78 °C and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (10 cm^3) was added followed by the ester **22** (1.9 g, 4.847 mmol) in dry THF (25 cm^3) over 10 min. After 1 h, methyl iodide (4 cm^3, 64 mmol) was added, and the mixture kept at −78 °C for 36 h, and then allowed to warm to −10 °C over 8 h. Aqueous ammonium chloride (saturated) was added and the mixture extracted with ether (3 × 100 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *ester* (1.824 mg, 93%); $[\alpha]_D^{22}$ −31.22 (*c* 2.29 in $CHCl_3$); R_f (EtOAc–hexane, 15:85) 0.38; ν_{max}(film)/cm^{-1} 1730 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.41 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 3.89–3.77 (1 H, m, CHO), 3.63–3.48 (1 H, m, CHO), 3.57 (3 H, s, OMe), 2.61 (1 H, dq, *J* 3.4 and 7, CHCO_2Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 1.60–1.14 (6 H, m, 3 × CH_2), 1.38 (3 H, s, *Me*$_A$-Me$_B$C), 1.35 (3 H, s, Me$_A$*Me*$_B$C), 1.09 (3 H, d, *J* 6.1, *Me*CHO), 1.04 (3 H, d, *J* 7, *Me*CHCO_2Me), 1.03–0.86 (1 H, m, SiCH) and 0.31 (6 H, s, $SiMe_2$); *m*/*z* 406 (1.8%, M$^+$), 391 (7.2, M − Me) and 149 (100, 4-MeC_6H_4SiMe$_2$) (Found: C, 67.96; H, 9.62; M$^+$, 406.2540. $C_{23}H_{38}O_4Si$ requires C, 67.94; H, 9.42%; *M*, 406.2539).

(2*S*,3*R*,6*R*,8*S*)-6,8-Dihydroxy-3-[dimethyl(4-methylphenyl)-silyl]-2-methylnonanoic acid

Pyridinium toluene-*p*-sulfonate (400 mg, 1.6 mmol) and the

ester **23** (1.824 g, 4.493 mmol) were refluxed in methanol (48 cm^3) for 2.5 h. Potassium hydroxide (85% in KOH, 5.6 g, 85 mmol) in methanol (20 cm^3), THF (20 cm^3) and water (10 cm^3) were added and the mixture was stirred at 40 °C for 15 h. The solvent was evaporated under reduced pressure and the residue was diluted with water (50 cm^3), acidified with hydrochloric acid (3 mol dm^{-1}) and extracted with ethyl acetate (3 × 100 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the *dihydroxy acid* (1.575 g, 99%); $[a]_D^{24}$ −14.9 (*c* 2.04 in $CHCl_3$); R_f (EtOAc) 0.16; ν_{max}(film)/cm^{-1} 3600–2500 (CO_2H and OH), 1700 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.16 (2 H, d, *J* 7.9, Ar), 5.56 (2 H, br s, 2 × OH), 4.03–3.82 (1 H, m, C*H*OH), 3.79–3.69 (1 H, m, C*H*OH), 2.64 (1 H, dq, *J* 2 and 7.3, MeC*H*CO_2Me), 2.33 (3 H, s, 4-*Me*C_6H_4), 1.63–1.14 (7 H, m, 3 × CH_2 and SiCH), 1.10 (3 H, d, *J* 6.2, *Me*CHOH), 1.07 (3 H, d, *J* 7.3, *Me*CHCO_2Me), 0.33 (3 H, s, Si*Me*$_A$Me$_B$) and 0.30 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 337 (3.1%, M − Me) and 149 (100, 4-MeC_6H_4-$SiMe_2$) (Found: M − Me, 337.1829. $C_{18}H_{29}O_4Si$ requires *M* − *Me*, 337.1835).

(2*S*,3*R*,6*R*,8*S*)-3-[Dimethyl(4-methylphenyl)silyl]-8-hydroxy-2-methylnonano-6-lactone 24

The dihydroxy acid (800 mg, 2.273 mmol) and triethylamine (3.25 cm^3, 23.2 mmol) in dichloromethane (400 cm^3) was added dropwise at reflux over 9 h to a stirred solution of 2-chloro-1-methylpyridinium iodide (3 g, 11.74 mmol) in dichloromethane (400 cm^3) under nitrogen. After a further 1 h under reflux, the solution was washed with water, with aqueous citric acid and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 4:6) to give the crude lactone (667 mg, 88%); cubes of the racemate (15 mg, 2%), mp 114–115 °C (from hexane), were deposited from hexane, enhancing the ratio of enantiomers to 98.2:1.8 and giving the *lactone* (652 mg, 86%); $[a]_D^{20}$ −63.87 (*c* 1.5 in $CHCl_3$); R_f (EtOAc–hexane, 4:6) 0.20; ν_{max}($CHCl_3$)/cm^{-1} 3600 (br, OH), 1720 (C=O), 1600 (Ar), 1250 (SiMe) and 1105 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.17 (2 H, d, *J* 7.9, Ar), 4.54–4.45 (1 H, m, CHOCO), 4.02–3.89 (1 H, m, C*H*OH), 3.00 (1 H, dq, *J* 2.6 and 7.0, MeC*H*CO_2), 2.34 (3 H, s, 4-*Me*C_6H_4), 2.13 (1 H, br s, OH), 2.08–1.55 (6 H, m, 3 × CH_2), 1.36 (1 H, td, *J* 5.3 and 2.6, SiCH), 1.20 (3 H, d, *J* 6.2, *Me*CHOH), 1.13 (3 H, d, *J* 7.0, *Me*CHCO_2), 0.40 (3 H, s, Si*Me*$_A$Me$_B$) and 0.36 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 334 (1.4%, M^+), 289 (65.3, M − MeCHOH) and 149 (100, 4-MeC_6H_4-$SiMe_2$) (Found: C, 68.17; H, 9.24; M^+, 334.1961. $C_{19}H_{30}O_3Si$ requires C, 68.22; H, 9.04%; *M*, 334.1964).

(2*S*,3*R*,6*R*,8*S*)-8-*tert*-Butyldimethylsilyloxy-3-[dimethyl(4-methylphenyl)silyl]-2-methylnonano-6-lactone

The alcohol **24** (1 g, 2.99 mmol), *tert*-butyldimethylsilyl chloride (1.5 g, 10 mmol) and imidazole (1.5 g, 20.83 mmol) were stirred in dimethylformamide (8 cm^3) at room temperature for 15 h. The mixture was poured into water and extracted with ether (3 × 50 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 5:95) to give the *silyl ether* (1.2 g, 90%); mp 63–64 °C (the crystals were freely soluble in common organic solvents, and could not be recrystallised); $[a]_D^{21}$ −43.63 (*c* 1.08 in $CHCl_3$); R_f (EtOAc–hexane, 1:9) 0.25; ν_{max}($CHCl_3$)/cm^{-1} 1720 (C=O), 1600 (Ar), 1250 (SiMe), 1100 (SiAr) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 7.38 (2 H, d, *J* 7.9, Ar), 7.17 (2 H, d, *J* 7.9, Ar), 4.49–4.39 (1 H, m, CHOCO), 3.93–3.85 (1 H, m, CHOSi), 2.96 (1 H, dq, *J* 2.6 and 7, MeC*H*CO_2), 2.34 (3 H, s, 4-*Me*C_6H_4), 1.99–1.72 (4 H, m, 2 × CH_2), 1.64–1.48 (2 H, m, CH_2), 1.38–1.33 (1 H, m, SiCH), 1.14 (3 H, d, *J* 6.5, *Me*CHOSi), 1.13 (3 H, d, *J* 7, *Me*CHCO_2), 0.86 (9 H, s, SiBu^t), 0.41 (3 H, s, Si*Me*$_A$Me$_B$), 0.37 (3 H, s, SiMe$_A$*Me*$_B$), 0.04 (3 H, s, OSi*Me*$_A$Me$_B$) and 0.02 (3 H, s, OSiMe$_A$*Me*$_B$); *m*/*z* 448 (0.2%, M^+), 391 (M − Bu^t) and 149 (100, 4-MeC_6H_4SiMe_2) (Found: C, 67.12; H, 9.71; M^+, 448.2838. $C_{25}H_{44}O_3Si_2$ requires C, 66.91; H, 9.88%; *M*, 448.2829).

Benzyl (2*S*,3*R*,6*R*,8*S*)-8-*tert*-butyldimethylsilyloxy-3-[dimethyl(4-methylphenyl)silyl]-6-hydroxy-2-methylnonanoate

Sodium benzyl oxide (0.5 mol dm^{-3} in benzyl alcohol, 5 cm^3) was added dropwise to a stirred solution of the silyl ether (1.17 g, 2.53 mmol) in THF (30 cm^3) and benzyl alcohol (15 cm^3) under nitrogen at room temperature, and the mixture kept for 6 h at room temperature. The solvent was evaporated off under reduced pressure. The residue was neutralised with aqueous ammonium chloride (saturated) and extracted with ether (2 × 100 cm^3). The extract was washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled under reduced pressure (0.5 mmHg) to remove benzyl alcohol and the residue was chromatographed (SiO_2, EtOAc–hexane, 15:85) to give the *hydroxy ester* (1.41 g, 97%); $[a]_D^{21}$ −8.13 (*c* 1.685 in $CHCl_3$); R_f (EtOAc–hexane, 15:85) 0.23; ν_{max}(film)/cm^{-1} 3520 (br, OH), 1730 (C=O), 1600 (Ar), 1250 (SiMe) and 1100 (SiAr); δ_H(250 MHz; $CDCl_3$) 7.40 (2 H, d, *J* 7.8, Ar), 7.35–7.29 (5 H, m, Ph), 7.15 (2 H, d, *J* 7.8, Ar), 5.01 (2 H, s, PhCH_2OCO), 3.97–3.89 (1 H, m, CHOSi), 3.57–3.45 (1 H, m, C*H*OH), 3.35 (1 H, d, *J* 1.2, OH), 2.64 (1 H, dq, *J* 3.4 and 7.2, MeC*H*CO_2), 2.33 (3 H, s, 4-*Me*C_6H_4), 1.59–1.16 (7 H, m, 3 × CH_2 and SiCH), 1.11 (3 H, d, *J* 6.1, *Me*CHOSi), 1.05 (3 H, d, *J* 7, *Me*CHCO_2), 0.88 (9 H, s, SiBu^t), 0.30 (6 H, s, $SiMe_2$), 0.09 (3 H, s, OSi*Me*$_A$Me$_B$) and 0.08 (3 H, s, OSiMe$_A$*Me*$_B$); *m*/*z* 556 (0.9%, M^+), 541 (M − Me), 465 (11, M − $PhCH_2$), 149 (65, 4-MeC_6H_4SiMe_2) and 91 (100, $PhCH_2$) (Found: C, 69.10; H, 9.53; M^+, 556.3395. $C_{32}H_{52}O_4Si_2$ requires C, 69.01; H, 9.41%; *M*, 556.3404).

Benzyl (2*S*,3*R*,6*R*,8*S*)-8-*tert*-butyldimethylsilyloxy-3-[dimethyl(4-methylphenyl)silyl]-6-(4-methylphenyl)sulfonyloxy-2-methylnonanoate

The hydroxy ester (1.4 g, 2.52 mmol), 4-dimethylaminopyridine (50 mg, 0.41 mmol) and toluene-*p*-sulfonyl chloride (2 g, 10.5 mmol) were kept in anhydrous pyridine (8 cm^3) at room temperature for 2 days. Crushed ice was added and the mixture extracted with hexane (3 × 50 cm^3). The extracts were washed with aqueous citric acid and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 1:9) to give the *tosylate* (1.735 g, 97%); $[a]_D^{21}$ −22.26 (*c* 3.02 in $CHCl_3$); R_f (EtOAc–hexane, 15:85) 0.41; ν_{max}($CHCl_3$)/cm^{-1} 1720 (C=O), 1600 (Ar), 1260 (SiMe), 1170 (OSO_2), 1105 (SiAr) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.3, Ar), 7.39–7.25 (9 H, m, Ar), 7.15 (2 H, d, *J* 7.7, Ar), 4.98 (2 H, s, PhCH_2OCO), 4.48–4.35 (1 H, m, CHOTs), 3.60–3.50 (1 H, m, CHOSi), 2.56 (1 H, dq, *J* 3.1 and 7, MeC*H*CO_2), 2.40 (3 H, s, 4-*Me*$C_6H_4SO_2$), 2.33 (3 H, s, 4-*Me*C_6H_4Si), 1.73 (1 H, td, *J* 6.8 and 13.8, CH_AH_BCHOSi), 1.50–1.07 (6 H, m, SiCH, CH_AH_BCHOSi and 2 × CH_2), 0.98 (3 H, d, *J* 5.7, *Me*CHOSi), 0.95 (3 H, d, *J* 7, *Me*CHCO_2), 0.83 (9 H, s, SiBu^t), 0.24 (3 H, s, Si*Me*$_A$Me$_B$), 0.23 (3 H, s, SiMe$_A$-*Me*$_B$), −0.03 (3 H, s, OSi*Me*$_A$Me$_B$) and −0.06 (3 H, s, OSiMe$_A$-*Me*$_B$) (Found: C, 65.94; H, 8.14. $C_{39}H_{58}O_6Si_2S$ requires C, 65.87; H, 8.22%).

Benzyl (−)-nonactate 25

The tosylate (1.735 g, 2.44 mmol), potassium bromide (335 mg, 2.8 mmol) and peracetic acid (36% w/v in AcOH, 25 cm^3) were stirred in acetic acid (20 cm^3) at room temperature for 15 h. The solvent was azeotropically evaporated with toluene under reduced pressure at room temperature. The residue was taken up in ethyl acetate and washed with water, with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 4:6) to give benzyl (−)-nonactate[24] (555 mg, 78%); $[a]_D^{22}$ −11.92 (*c* 1.93 in $CHCl_3$); R_f (EtOAc–hexane,

15:85) 0.25; ν_{max}($CDCl_3$)/cm^{-1} 3500 (OH), 1730 (C=O); δ_H(400 MHz; $CDCl_3$) 7.35–7.26 (5 H, m, Ph), 5.15 (1 H, d, *J* 12.4, PhC$H_A$$CH_B$O), 5.12 (1 H, d, *J* 12.4, PhCH_ACH_BO), 4.14–4.05 (1 H, m, CHO), 4.04–3.94 (2 H, m, CHO and C*H*OH), 2.7 (1 H, br s, OH), 2.58 (1 H, quintet, *J* 7.1, MeC*H*CO_2), 1.99–1.92 (2 H, m, CH_2), 1.73–1.54 (4 H, m, 2 × CH_2), 1.17 (3 H, *J* 6.3, *Me*CHOH) and 1.13 (3 H, *J* 7.1, *Me*CHCO_2); δ_C(100 MHz; $CDCl_3$) 174.6, 136.1, 128.5, 128.2, 128.1, 80.9, 77.1, 66.2, 65.2, 45.4, 43.1, 30.7, 28.7, 23.3 and 13.5.

The benzyl (−)-nonactate (10 mg) was hydrogenolysed with 10% Pd/C in THF and esterified with ethereal diazomethane. The enantiomeric purity of this methyl (−)-nonactate was checked (GC, as with the dextrorotatory enantiomer) and appeared to be 100%.

Methyl (2*S*,3*S*,6*R*,8*R*)-8-*O*-*tert*-butyldimethylsilylnonactate

Methyl (+)-nonactate **4** (520 mg, 2.4 mmol), *tert*-butyldimethylsilyl chloride (910 mg, 6 mmol) and imidazole (900 mg, 12.5 mmol) were stirred in dimethylformamide (5 cm^3) at room temperature for 15 h. The mixture was poured into water and extracted with ether (3 × 50 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 10:90) to give the silyl ether[26] (790 mg, 99%); R_f (EtOAc–hexane, 1:9) 0.29; $[\alpha]_D^{21}$ −18.84 (*c* 1.47 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 3.97–3.83 (3 H, m, CHOSi and 2 × CHO), 3.67 (3 H, s, CO_2Me), 2.48 (1 H, dq, *J* 8.3 and 7, MeC*H*CO_2Me), 1.97–1.87 (2 H, m, CH_2), 1.59–1.39 (4 H, m, 2 × CH_2), 1.11 (3 H, d, *J* 6.1, *Me*CHOSi), 1.10 (3 H, d, *J* 7, *Me*CHCO_2Me), 0.86 (9 H, s, SiBu^t), 0.03 (3 H, s, Si*Me*$_A$Me$_B$) and 0.02 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 331 (1.5%, M + H), 315 (1, M − Me), 299 (4.2, M − OMe), 273 (65, M − Bu^t), 220 (100) and 75 (83, Me_2SiOH) (Found: M + H, 331.2283. $C_{17}H_{35}O_4Si$ requires *M* + H, 331.2305).

(2*S*,3*S*,6*R*,8*R*)-8-*O*-*tert*-Butyldimethylsilylnonactic acid 26

Potassium hydroxide (5 mol dm^{-3} in H_2O, 3 cm^3) was stirred with the ester (720 mg, 2.18 mmol) in THF (9 cm^3) and methanol (3 cm^3) at room temperature for 15 h. The mixture was evaporated under reduced pressure. The residue was diluted with water, acidified with aqueous citric acid (10%) and extracted with ether (3 × 50 cm^3). The extract was washed with water and with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the acid[26] (685 mg, 99%); R_f (EtOAc–hexane, 4:6) 0.38; $[\alpha]_D^{21}$ −31.97 (*c* 1.73 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3300–2500 (br, COOH), 1730 (C=O) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 4.09–3.84 (3 H, m, CHOSi and 2 × CHO), 2.49 (1 H, quintet, *J* 7, MeC*H*CO_2Me), 2.07–1.91 (2 H, m, CH_2), 1.68–1.48 (4 H, m, 2 × CH_2), 1.18 (3 H, d, *J* 7, *Me*CHCO$_2$Me), 1.13 (3 H, d, *J* 6.1, *Me*CHOSi), 0.88 (9 H, s, SiBu^t), 0.04 (3 H, s, Si*Me*$_A$Me$_B$) and 0.03 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 317 (1.2%, M + H), 301 (0.6, M − Me), 259 (48, M − Bu^t) and 75 (100, $SiMe_2OH$) (Found: C, 60.94; H, 10.07. $C_{16}H_{32}O_4Si$ requires C, 60.71; H, 10.19%).

Benzyl (2′*S*,3′*S*,6′*R*,8′*R*)-8′-*O*-*tert*-butyldimethylsilyl-8-nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactate 27

The acid **26** (575 mg, 1.82 mmol), alcohol **25** (530 mg, 1.82 mmol), dicyclohexylcarbodiimide (391 mg, 1.9 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) were stirred in dichloromethane (10 cm^3) for 12 h at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in ether, filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 15:85) to give the *ester* (1 g, 93%); R_f (EtOAc–hexane, 2:8) 0.35; $[\alpha]_D^{21}$ −9.62 (*c* 1.71 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O) and 840 (OSi); δ_H(400 MHz; $CDCl_3$) 7.35–7.27 (5 H, m, Ph), 5.15 (1 H, d, *J* 12.4, PhC$H_A$$H_B$OCO), 5.11 (1 H, d, *J* 12.4, PhC$H_A$$H_B$OCO), 4.99–4.90 (1 H, m, MeC*H*OCO), 4.04–3.82 (5 H, m, MeC*H*OSi and 4 × CHO), 2.55 (1 H, quintet, *J* 7, MeC*H*CO_2), 2.45 (1 H, quintet, *J* 7.1, MeC*H*CO_2), 2.02–1.85 (4 H, m, 2 × CH_2), 1.81–1.40 (8 H, m, 4 × CH_2), 1.19 (3 H, d, *J* 7.1, *Me*CHCO$_2$), 1.11 (3 H, d, *J* 7, *Me*CHCO$_2$), 1.10 (3 H, d, *J* 6.1, *Me*CHO), 1.07 (3 H, d, *J* 7, *Me*CHO), 0.86 (9 H, s, SiBu^t) and 0.03 (6 H, s, $SiMe_2$); δ_C(100 MHz; $CDCl_3$) 174.63, 174.21, 136.22, 128.50, 128.06, 80.27, 80.01, 76.71, 76.34, 69.31, 66.26, 66.12, 46.15, 45.70, 45.43, 42.54, 31.52, 31.49, 28.44, 28.39, 25.92, 24.68, 20.59, 18.08, 13.24, 13.16, −4.50 and −4.79; *m*/*z* 533 (1.3%, M − Bu^t) and 91 (100, $PhCH_2$) (Found: C, 67.44; H, 9.34. $C_{33}H_{54}O_7Si$ requires C, 67.08; H, 9.21%).

Benzyl (2′*S*,3′*S*,6′*R*,8′*R*)-8-nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactate 28

The silyl ether **27** (59 mg, 0.1 mmol) and toluene-*p*-sulfonic acid monohydrate (3 mg, 0.016 mmol) were stirred in acetic acid (0.45 cm^3) and water (0.05 cm^3) at room temperature for 30 min. The mixture was evaporated under vacuum and diluted with ether. The ether solution was washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 1:1) to give the alcohol[24] (47 mg, 98%); R_f (EtOAc–hexane, 1:1) 0.25; $[\alpha]_D^{20}$ +8.43 (*c* 1.63 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3500 (br, OH) and 1730 (C=O); δ_H(400 MHz; $CDCl_3$) 7.35–7.27 (5 H, m, Ph), 5.15 (1 H, d, *J* 12.4, PhC$H_A$$H_B$OCO), 5.11 (1 H, d, *J* 12.4, PhC$H_A$$H_B$OCO), 5.02–4.94 (1 H, m, MeC*H*OCO), 4.12–3.83 (5 H, m, MeC*H*OH and 4 × CHO), 2.81 (1 H, d, *J* 3.7, OH), 2.56 (1 H, quintet, *J* 7, MeC*H*CO_2), 2.47 (1 H, quintet, *J* 7.1, MeC*H*CO_2), 2.02–1.85 (4 H, m, 2 × CH_2), 1.80–1.43 (8 H, m, 4 × CH_2), 1.20 (3 H, d, *J* 6.2, *Me*CHO), 1.17 (3 H, d, *J* 6.3, *Me*CHO), 1.10 (3 H, d, *J* 7.2, *Me*CHCO$_2$) and 1.09 (3 H, d, *J* 7.2, *Me*CHCO$_2$); δ_C(100 MHz; $CDCl_3$) 174.71, 174.18, 136.22, 128.49, 128.08, 80.88, 80.36, 76.49, 69.49, 66.14, 65.11, 45.50, 45.47, 43.02, 42.49, 31.41, 30.66, 28.60, 28.44, 23.35, 20.56, 13.30 and 13.27.

(2′*S*,3′*S*,6′*R*,8′*R*)-8-Nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactic acid

The ester **28** (112 mg, 0.235 mmol) was stirred with palladium (10% on charcoal, 10 mg) in THF (5 cm^3) under hydrogen for 10 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the acid[26] (90 mg, 99%); R_f (EtOAc) 0.12; $[\alpha]_D^{21}$ +12.42 (*c* 0.77 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3500 (OH), 3500–2500 (br, COOH) and 1720 (C=O); δ_H(250 MHz; $CDCl_3$) 5.59 (2 H, br, OH and COOH), 5.01 (1 H, apparently sextet, *J* 6.3, MeC*H*OCO), 4.19–4.08 (1 H, m, MeC*H*OH), 4.07–3.90 (4 H, m, 4 × CHO), 2.53–2.43 (2 H, m, 2 × MeC*H*CO_2), 2.06–1.90 (4 H, m, 2 × CH_2), 1.79–1.55 (8 H, m, 4 × CH_2), 1.22 (3 H, d, *J* 6.3, *Me*CHO), 1.18 (3 H, d, *J* 6.3, *Me*CHO), 1.14 (3 H, d, *J* 7.0, *Me*CHCO$_2$) and 1.09 (3 H, d, *J* 7.0, *Me*CHCO$_2$); δ_C(100 MHz; $CDCl_3$) 177.12, 174.33, 81.06, 80.49, 76.66, 69.00, 65.20, 45.46, 44.97, 42.80, 42.32, 31.11, 30.54, 29.08, 28.76, 23.17, 20.32, 13.65 and 13.44.

Benzyl (2‴*S*,3‴*S*,6‴*R*,8‴*R*)-8‴-*O*-*tert*-butyldimethylsilyl-8″-nonactinoyl-(2″*R*,3″*R*,6″*S*,8″*S*)-8′-nonactinoyl-(2′*S*,3′*S*,6′*R*,8′*R*)-8-nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactate

The ester **27** (354 mg, 0.6 mmol) was stirred with palladium (10% on charcoal, 25 mg) in THF (6 cm^3) under hydrogen for 10 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give (2′S,3′S,6′R,8′R)-8′-O-tert-*butyldimethylsilylnonactinoyl*-(2R,3R,6S,8S)-*nonactic acid* **29** (300 mg, 100%); R_f (EtOAc–hexane, 4:6) 0.14; $[\alpha]_D^{21}$ −8.12 (*c* 1.65 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3500–2500 (br, COOH), 1730 (C=O) and 840 (OSi); δ_H(250 MHz; $CDCl_3$) 5.10–4.95 (1 H, m, MeC*H*OCO), 4.05–3.80 (5 H, m, MeC*H*OSi and 4 × CHO), 2.55–2.40 (2 H, m, 2 × MeC*H*CO_2), 2.07–1.40 (12 H, m, 6 × CH_2), 1.24 (3 H, d, *J* 6.3, *Me*CHO), 1.17 (3 H, d, *J* 7.1, *Me*CHCO$_2$), 1.10 (3 H, d, *J* 6.3, *Me*CHO), 1.07 (3 H, d, *J* 7.6, *Me*CHCO$_2$), 0.86 (9 H, s, SiBu^t) and 0.03 (6 H, s, $SiMe_2$).

Following Yamaguchi,[27] 2,4,6-trichlorobenzoyl chloride (11×10^{-3} cm^3, 0.07 mmol) was added with stirring to a mixture of the acid **29** (27 mg, 0.053 mmol), the alcohol **28** (25 mg, 0.053 mmol) and 4-dimethylaminopyridine (25 mg, 0.2 mmol) in dichloromethane (0.5 cm^3) under argon at room temperature, and the mixture kept for 12 h. The solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (25 cm^3) and washed with aqueous citric acid (10%), with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–toluene, 30:70) to give the *ester* (48 mg, 95%); R_f (EtOAc–hexane, Et_2O–hexane, 6:4) 0.4; $[\alpha]_D^{20}$ −6.58 (*c* 1.19, $CDCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 1730 (C=O) and 840 (OSi); δ_H(400 MHz; $CDCl_3$) 7.34–7.26 (5 H, m, Ph), 5.14 (1 H, d, *J* 12.4, PhCH_AH$_B$OCO), 5.10 (1 H, d, *J* 12.4, PhCH$_A$$H_B$OCO), 5.00–4.90 (3 H, m, 3 × MeC*H*OCO), 4.04–3.79 (9 H, m, MeC*H*OSi and 8 × CHO), 2.55 (1 H, quintet, *J* 7, MeC*H*CO$_2$), 2.49–2.40 (3 H, m, 3 × MeC*H*CO$_2$), 2.01–1.40 (24 H, m, 12 × CH$_2$), 1.21 (3 H, d, *J* 6.2, *Me*CHO), 1.20 (3 H, d, *J* 6.3, *Me*CHO), 1.18 (3 H, d, *J* 6.3, *Me*CHO), 1.10 (3 H, d, *J* 7.1, *Me*CHCO$_2$), 1.09 (3 H, d, *J* 6.0, *Me*CHO), 1.06 (3 H, d, *J* 7.0, *Me*CHCO$_2$), 1.05 (6 H, d, *J* 7.0, 2 × *Me*CHCO$_2$), 0.86 (9 H, s, SiBu^t) and 0.02 (6 H, s, SiMe$_2$); δ_C(100 MHz; $CDCl_3$) 174.65, 174.17, 174.12, 174.06, 136.22, 128.48, 128.05, 80.30, 80.14, 80.08, 80.00, 76.68, 76.61, 76.33, 69.37, 69.30, 66.25, 66.10, 46.15, 45.68, 45.52, 45.48, 45.45, 42.51, 31.54, 31.51, 31.44, 28.44, 28.38, 28.17, 25.92, 24.68, 20.62, 20.58, 18.08, 13.26, 13.17, 12.98, 12.94, −4.50 and −4.79 (Found: C, 66.51; H, 9.08. $C_{53}H_{86}O_{13}Si$ requires C, 66.35; H, 9.04%).

(2‴*S*,3‴*S*,6‴*R*,8‴*R*)-8″-Nonactinoyl-(2″*R*,3″*R*,6″*S*,8″*S*)-8′-nonactinoyl-(2′*S*,3′*S*,6′*R*,8′*R*)-8-nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactic acid 30

The ester (255 mg, 0.267 mmol) was stirred with palladium (10% on charcoal, 15 mg) in THF (4 cm^3) under hydrogen for 10 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give (2‴S,3‴S,6‴R,8‴R)-8-O-*tert*-*butyldimethylsilyl*-8″-*nonactinoyl*-(2″R,3″R,6″S,8″S)-8′-*nonactinoyl*-(2′S,3′S,6′R,8′R)-8-*nonactinoyl*-(2R,3R,6S,8S)-*nonactic acid* (220 mg, 95%); R_f (Et_2O) 0.23; $[\alpha]_D^{20}$ −4.82 (*c* 0.85 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500–2500 (br, COOH), 1730 (C=O) and 840 (OSi); δ_H(400 MHz; $CDCl_3$) 5.03–4.89 (3 H, m, 3 × MeC*H*OCO), 4.00–3.80 (9 H, m, MeC*H*OSi and 8 × CHO), 2.50–2.39 (4 H, m, 4 × MeC*H*CO$_2$), 2.01–1.36 (24 H, m, 12 × CH$_2$), 1.21 (3 H, d, *J* 6.3, *Me*CHO), 1.20 (3 H, d, *J* 6.1, *Me*CHO), 1.19 (3 H, d, *J* 6.2, *Me*CHO), 1.13 (3 H, d, *J* 7.1, *Me*CHCO$_2$), 1.09 (3 H, d, *J* 6.1, *Me*CHO), 1.05 (9 H, d, *J* 7, 3 × *Me*CHCO$_2$), 0.85 (9 H, s, SiBu^t) and 0.01 (6 H, s, SiMe$_2$); δ_C(100 MHz; $CDCl_3$) 177.34, 174.41, 174.22, 174.17, 80.33, 80.08, 80.00, 76.95, 76.67, 76.52, 76.36, 69.31, 68.93, 66.27, 46.12, 45.68, 45.60, 45.53, 44.96, 42.50, 42.40, 31.51, 31.39, 31.16, 29.69, 29.01, 28.37, 28.18, 25.91, 24.67, 20.61, 20.43, 18.07, 13.36, 13.28, 13.16, 12.97, −4.50 and −4.79. The acid and toluene-*p*-sulfonic acid (12 mg, 0.035 mmol) were kept at room temperature in acetic acid (1.8 cm^3) and water (0.2 cm^3) for 1 h. The solvent was azeotropically evaporated under reduced pressure. The residue was dissolved in ethyl acetate (30 cm^3) and washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the hydroxy acid[24] (190 mg, 100%); R_f (EtOAc-MeOH, 98:2) 0.12; $[\alpha]_D^{21}$ +5.14 (*c* 1.99 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 3500–2500 (br, COOH) and 1715 (C=O); δ_H(400 MHz; $CDCl_3$) 5.03–4.89 (3 H, m, 3 × MeC*H*OCO), 4.15–3.78 (9 H, m, MeC*H*OH and 8 × CHO), 2.50–2.40 (4 H, m, 4 × MeC*H*CO$_2$), 2.01–1.45 (24 H, m, 12 × CH$_2$), 1.20 (3 H, d, *J* 6.1, *Me*CHOCO), 1.19 (6 H, d, *J* 6.1, 2 × *Me*CHOCO), 1.16 (3 H, d, *J* 6.1, *Me*CHOCO), 1.11 (3 H, d, *J* 7, *Me*CHCO), 1.06 (3 H, d, *J* 7, *Me*CHCO), 1.04 (3 H, d, *J* 7, *Me*CHCO) and 1.03 (3 H, d, *J* 7, *Me*CHCO); δ_C(100 MHz; $CDCl_3$) 177.28, 174.33, 174.21, 174.19, 80.87, 80.29, 80.17, 80.15, 76.96, 76.87, 76.53, 76.44, 69.48, 69.35, 68.99, 65.11, 45.55, 45.52, 44.85, 43.11, 42.44, 42.34, 31.43, 31.39, 31.22, 30.66, 28.80, 28.60, 28.34, 28.17, 23.27, 20.57, 20.41, 13.33, 13.21 and 13.00.

Nonactin 31 from the acid 30

2,4,6-Trichlorobenzoyl chloride (0.028 cm^3, 0.18 mmol) was added with stirring to the hydroxy acid **30** (97 mg, 0.129 mmol) and 4-dimethylaminopyridine (60 mg, 0.5 mmol) in dichloromethane (45 cm^3) with molecular sieves (4 Å, powdered, 1.5 g) under argon at room temperature, and kept for 12 h. The mixture was filtered and the filtrate was washed with dilute hydrochloric acid, with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–hexane, 40:60) to give nonactin (78 mg, 82%). Crystallisation from ether gave nonactin (69 mg, 73%); mp 146–147 °C (lit.,[24] 149–150 °C); R_f (EtOAc–hexane, 4:6) 0.27; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ_H(400 MHz; $CDCl_3$) 4.95 (4 H, sextet, *J* 6.5, 4 × MeC*H*OCO), 3.99 (4 H, quartet, *J* 7.2, 4 × CHO), 3.83 (4 H, quintet, *J* 6.5, 4 × CHO), 2.48 (4 H, quintet, *J* 7.2, 4 × MeC*H*CO$_2$), 2.01–1.87 (8 H, m, 4 × CH$_2$), 1.81–1.66 (8 H, m, 4 × CH$_2$), 1.65–1.42 (8 H, m, 4 × CH$_2$), 1.21 (12 H, d, *J* 6.2, 4 × *Me*CHOCO) and 1.07 (12 H, d, *J* 7, 4 × *Me*CHCO); δ_C(100 MHz; $CDCl_3$) 174.24, 80.04, 76.35, 69.06, 45.24, 42.27, 31.39, 28.14, 20.50 and 12.84.

Nonactin 31 from (2′*S*,3′*S*,6′*R*,8′*R*)-8-nonactinoyl-(2*R*,3*R*,6*S*,8*S*)-nonactic acid

Similarly, the hydroxy acid (37 mg, 0.096 mmol), 2,4,6-trichlorobenzoyl chloride (0.02 cm^3, 0.12 mmol) and 4-dimethylaminopyridine (37 mg, 0.3 mmol) in dichloromethane (25 cm^3) with molecular sieves gave nonactin (contaminated with cyclic dimer and cyclic hexamer) (32 mg, 88%). Crystallisation from ether gave nonactin (15 mg, 41%); mp 146–147 °C; identical (mp, TLC, IR, ^{1}H NMR) with the earlier sample. The mother liquor was rechromatographed and crystallised to give a second crop (3.5 mg, 11%) (52% overall) and a mixture of cyclic dimer and hexamer (about 25%).

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