# The total synthesis of the diepoxycyclohexanone antibiotic aranorosin and novel synthetic analogues

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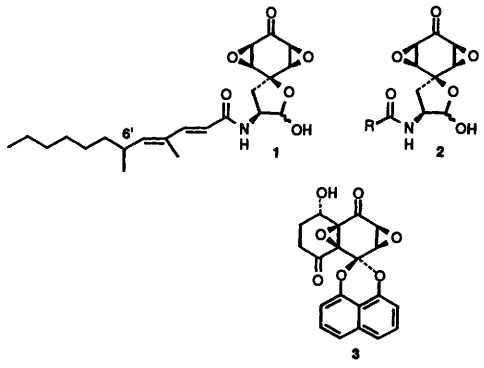
**A short synthesis of the novel antibiotic aranorosin in chiral form is described which employs (i) a novel hypervalent iodine-mediated oxidative hydroxylation of a tyrosinal derivative and (ii) a stereocontrolled *cis*-bisepoxidation in the key steps. A similar procedure was employed to prepare 6′-epiaranorosin, and hence establish the stereochemistry of the natural compound, and to prepare novel aranorosin analogues. An organometallic route is described which gives desamidoaranorosin.**

Aranorosin **1** was isolated from the fungal strain *Pseudoarachniotus roseus* in 1988[1] and shown to possess antibiotic, antifungal and antineoplastic activity.[1,2] The gross structure of aranorosin, together with the relative stereochemistry around the tetracyclic nucleus, was determined by NMR spectroscopy, mass spectrometry and chemical studies, but the configuration of the side chain C-6′ methyl substituent and its absolute stereochemistry were not established.[1] The highly challenging structure of aranorosin, combined with its range of biological activities, has attracted considerable synthetic interest, both from our group[3–6] and others.[7–9] We now report the full details of a concise total synthesis of aranorosin, thereby establishing its absolute stereochemistry,[6] together with the synthesis of 6′-epiaranorosin and several other novel, *N*-acyl analogues **2** of the natural compound. An alternative total synthesis of aranorosin has been published by Wipf, Kim and Fritch and their structural deductions[9] are consistent with ours. Also of relevance is the recent discovery of a large family of related diepoxycyclohexanones, exemplified by diepoxin α **3**, which also contain the *cis*-disposed epoxide rings.[10]

The retrosynthetic analysis adopted in this study is shown in Scheme 1. Amide disconnection gave acid **4** and the key tetracyclic synthon **5**, which in turn appeared accessible from cyclohexadienone **6**. Tyrosine **7** seemed an ideal, chiral pool precursor to intermediate **6**, and indeed would seem to be the likely biogenetic starting point too. However, preliminary studies (see later)[3] indicated that this 'biomimetic' approach presented difficulties in terms of the stereoselective generation of the required all *cis*-oxygenation pattern. An alternative approach to **5** was therefore investigated which commenced with Swenton's quinone monoacetal **8**.[11] This 'organometallic' approach required the addition of a nucleophilic alanine equivalent **9** to ketone **8** followed by stereoselective *cis*-bisepoxidation. Although this approach has not been progressed to prepare aranorosin, it did lead to a successful synthesis of the key tetracyclic aranorosin nucleus, and also established guidelines to underpin the successful approach *via* the biomimetic route.




### Organometallic approach

Following model studies which demonstrated that 4-substituted 4-quinols undergo stereoselective *cis*-bisepoxidation with alkaline hydrogen peroxide,[4] this methodology was applied to the preparation of the aranorosin analogue **15** as shown in Scheme 2. The Grignard reagent **10** derived from 3-bromopropanal ethylene acetal[12] underwent efficient addition to **8** to give adduct **11** which, after selective acetal hydrolysis, gave dienone **12** in 48% overall yield from **8** (72% based on recovered starting material). Epoxidation of dienone **12** using conditions developed in the model studies[4] gave only the *cis*-bisepoxide **13**. The structure of **13** was confirmed by high field NMR spectroscopy (symmetrical oxiranyl protons in $^1$H NMR spectrum at $\delta$ 3.48–3.52). Attempted acetal hydrolysis under acidic conditions gave only low yields of the desired lactol **15**. The use of $PdCl_2$·$(MeCN)_2$[13] in anhydrous acetone with a 3 h reaction time gave the dimeric product **14** in high yield but again acidic hydrolysis of **14** to **15** proved inefficient. It was eventually discovered that the use of $PdCl_2$·$(MeCN)_2$[13] in aqueous acetone, though slow, gave a reasonable (61%) conversion to **15**. An alternative route to **15**, using similar chemistry and involving organometallic butenyl addition followed by ozonolysis, was also devised (Scheme 2).[5] The structure of **15** was confirmed by 400 MHz NMR spectroscopy, large W coupling being observed between $H_a$–$H_b$ (2.7 Hz) and $H_c$–$H_d$ (4 Hz). In addition, a strong NOE was observed between $H_c$ and $H_d$ and the nearby tetrahydrofuranyl methylene protons. The structure has also been confirmed by X-ray crystallography.[14] Aranorosin analogue **15** displays a low level of antibiotic activity (100 mg ml$^{-1}$) against a range of Gram-negative bacilli and against *Staphylococcus aureus*. Preliminary studies were conducted to devise a synthetic equivalent of the nucleophilic alanine synthon **9**. However, success with the biomimetic approach resulted in all efforts being concentrated in that area.

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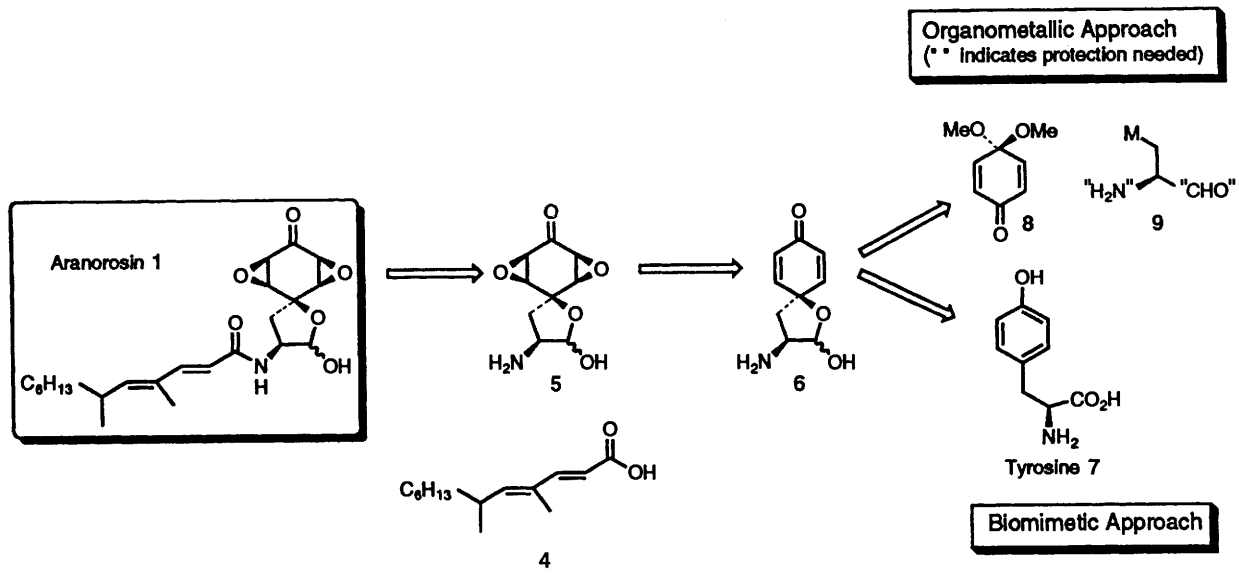
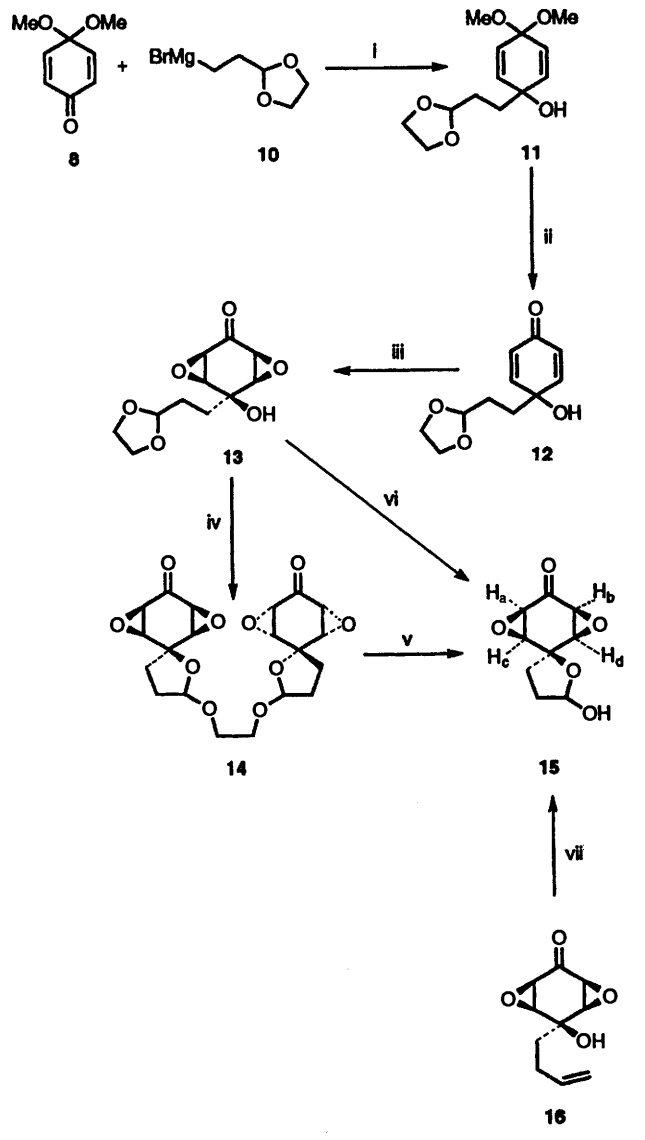
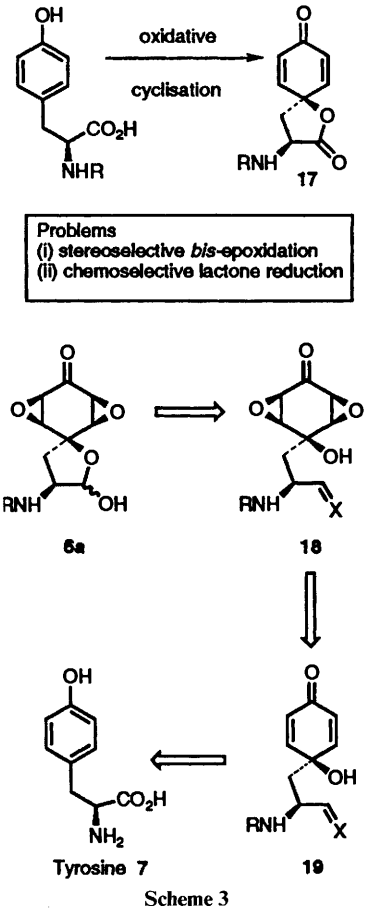



Scheme 1



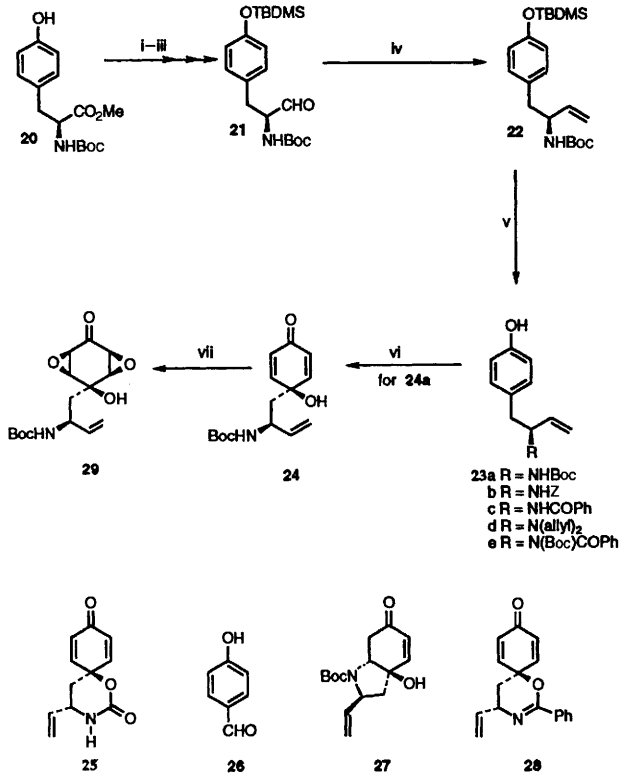




Scheme 3

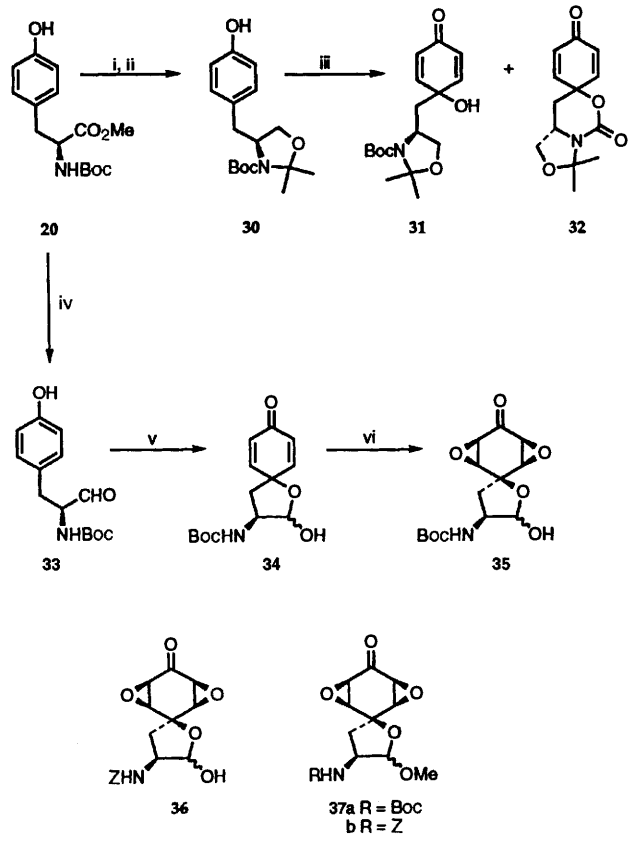
**Scheme 2** *Reagents and conditions:* i, THF, −78 °C; ii, oxalic acid, $SiO_2$, $CH_2Cl_2$ (48% from **8**, 72% based on recovered starting material); iii, $H_2O_2$, NaOH, MeOH then mol. sieves, EtOAc (69%); iv, $PdCl_2$·$(MeCN)_2$, acetone, 3 h (86%); v, aq. $H_2SO_4$, $SiO_2$, $CH_2Cl_2$ (18%); vi, $PdCl_2$·$(MeCN)_2$, aq. acetone, 3 d (61%); vii, $O_3$, $CH_2Cl_2$ then $Me_2S$ (76%) (ref. 5)

**Biomimetic approach**

In common with the groups of Rama Rao [7] and Wipf [8,9] we initially approached the synthesis of aranorosin *via* the oxidative cyclisation [15] of tyrosine derivatives to give spirolactones of type **17**.[3] It soon became apparent, however,[3,7] that the selective elaboration of such compounds (*e.g.* stereocontrolled epoxidation and regioselective lactone reduction) was not a straightforward task (although Wipf *et al.* devised an elegant solution to this problem [8,9]). On the basis of these observations and the model studies discussed earlier (Scheme 2) we decided to further refine the retrosynthetic plan as shown in Scheme 3. Thus, *para*-quinol **19** was designated the




**Scheme 4** *Reagents and conditions:* i, TBDMSCl, imidazole (86%); ii, $LiAlH_4$, THF (100%); iii, oxalyl chloride, DMSO (94%); iv, $Ph_3PCH_3Br$, KHMDS, THF (68%); v, TBAF, THF (96%); vi, PIDA, aq. MeCN, 0 °C (see text); vii, $H_2O_2$, NaOH (25%)

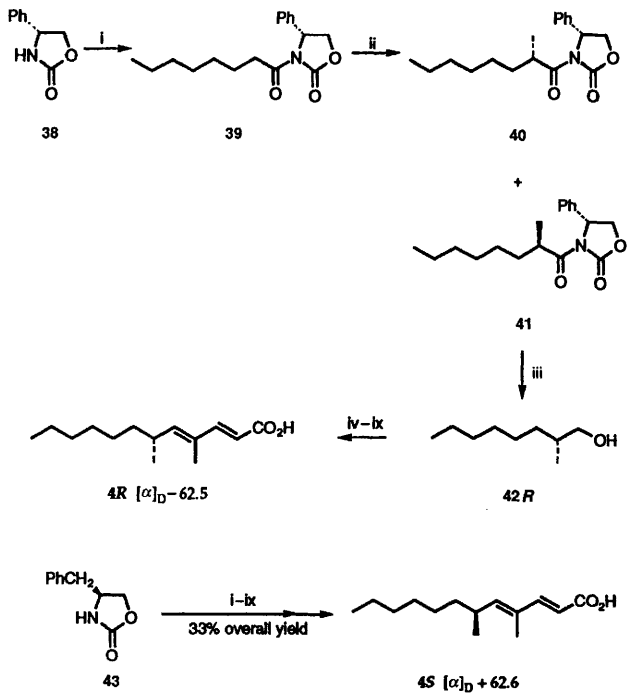



**Scheme 5** *Reagents and conditions:* i, $NaBH_4$, $CaCl_2$ (99%); ii, 2,2-dimethoxypropane, acetone, PTSA (91%); iii, PIDA, aq. MeCN (**31**, 20–37%; **32**, 13–22%); iv, DIBAL-H, −78 °C (88%); v, PIFA, aq. MeCN (35%); vi, $H_2O_2$, NaOH (45%)

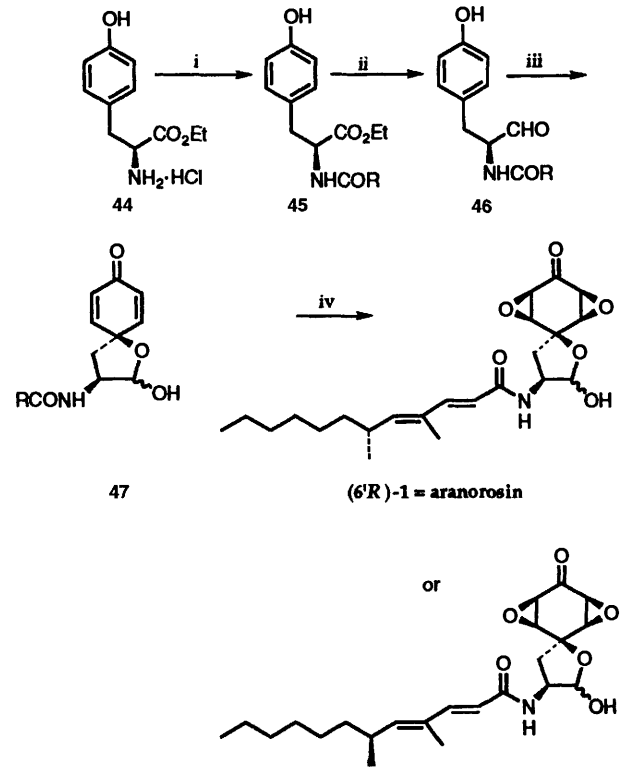
key intermediate: it has the α-amino function at the required oxidation level and the presence of the 4-hydroxy substituent seemed likely to ensure that *cis*-bisepoxidation occurred smoothly to give **18**. Two variants were considered based on **19** (X = $CH_2$) and **19** (X = O). The latter seemed to be complicated by the equilibrium of the hydroxy aldehyde and lactol and so the former was investigated first (Scheme 4).

The protected tyrosine derivative **20**[16] was efficiently converted into the tyrosinal **21** using the sequence published for the enantiomeric series.[17] Methylenation of aldehyde **21** using $CH_2I_2$–$Me_3Al$–Zn, which has been successfully employed to homologate alkyl amino aldehydes without epimerisation,[18] gave a moderate yield of alkene **22** but in racemic form. However, the use of salt-free Wittig conditions,[19] gave **22** in 80% yield with minimal racemisation {$[\alpha]_D$ +23 (*c* 0.7, $CHCl_3$); NMR spectroscopic analysis of the Mosher amide derived from **22** after removal of the Boc protecting group indicated a diastereoisomeric excess (de) of 96%}. Cleavage of the silyl ether with tetrabutylammonium fluoride (TBAF) gave the phenol **23a** in 96% yield as a colourless solid {mp 70–72 °C, $[\alpha]_D$ +28.3 (*c* 2.5, $CHCl_3$)}. Phenol **23a** was converted into the desired quinol **24** using iodobenzene bis(trifluoroacetate) (PIFA) or iodobenzene diacetate (PIDA) in aqueous acetonitrile.[20] Disappointingly, **24** was obtained in low yield (3–12%), accompanied by the oxazolinone **25** (20–50%), and *p*-hydroxybenzaldehyde **26**,[21] which was isolated in variable yield. In one reaction azabicycle **27** was isolated in 15% yield, presumably formed by cyclisation of **24**. In general, PIDA was found to give higher yields of the dienone than PIFA, but attempted optimisation failed to give satisfactory yields. The *N*-Z, *N*-Bz and *N*,*N*-diallyl compounds **23b–d** were prepared by similar procedures and were also subjected to PIDA or PIFA oxidation. The Z derivative **23b** gave modest yields of the desired quinol (16–20% using PIDA); the benzoyl analogue **23c** gave no quinol but a 45% yield of dienone **28** using PIFA; the *N*,*N*-diallylamine **23d** and the *N*-benzoyl-*N*-Boc analogue **23e** gave no isolable products. In order to establish the viability of this general approach, dienone **24** was epoxidised using hydrogen peroxide in methanolic sodium hydroxide, which gave the desired *cis*-bisepoxide **29** in 25%, unoptimised yield.

Attention was therefore concentrated on the elaboration of tyrosine derivatives rather than their homologated variants (Scheme 5). Protected tyrosinol **30**[22] was investigated first. Oxidation of **30** with PIDA in aqueous acetonitrile gave, after chromatography, the required dienone **31** in 20–37% yield, accompanied by the oxazolinone **32** (13–22%). The disappointing yields obtained in the oxidation of masked tyrosine aldehydes and alcohols prompted us to investigate the direct hypervalent iodine oxidation of appropriate tyrosinals in aqueous solvent (Scheme 5). *N*-Boc protection was chosen initially in the hope that compound **35** could be obtained as a versatile precursor to aranorosin and novel analogues by a deprotection–acylation sequence. The tyrosinal **33** was prepared directly from the Boc ester **20** using 4 equivalents of diisobutylaluminium hydride DIBAL-H in THF at −78 °C (phenol protection was not required) and was subjected to PIFA oxidation in aqueous acetonitrile at 0 °C. The product dienone **34** was isolated as a mixture of lactols in 34% yield. Epoxidation of the dienone **34** gave the required, unstable diepoxide **35** in 45% yield as a 2:1 equilibrium mixture of lactol isomers. Comparison of spectral data with those reported for aranorosin confirmed that the required *cis*-bisepoxidation had been achieved in a stereoselective manner. This result showed that the directed epoxidation could be carried out on lactols such as **34** as well as on compounds bearing a 'free' hydroxy substituent at C-4 (*e.g.* **12**). Carbamate **36** was prepared in a similar manner, again with the epoxidation proceeding stereoselectively, but all attempts to deprotect and then acylate, or *vice versa*, carbamates **35** and **36** were unsuccessful, presumably for reasons of steric hindrance, and none of the desired amide could be isolated. A similar lack of success was



**Scheme 6** *Reagents and conditions:* i, BuLi, then $C_7H_{15}COCl$ (94%); ii, NaHMDS, MeI (quant.; **40**:**41**, 13:87); iii, $LiBH_4$, aq. $Et_2O$ (88%); iv, oxalyl chloride, DMSO (quant.); v, $Ph_3P{=}C(Me)CO_2Et$ (84%); vi, DIBAL-H (98%); vii, $MnO_2$ (quant.); viii, $Ph_3P{=}CHCO_2Et$ (87%); ix, LiOH, aq. THF–MeOH (81%)



**Scheme 7** (R = *R* or *S*,*E*,*E*-$C_6H_{13}CHMeCH{=}CMeCH{=}CH$–). *Reagents and conditions:* i, **4**, $Ph_2POCl$, $Et_3N$, THF, rt [(6′*R*)-**45**, 73%; (6′*S*)-**45**, 81%]; ii, DIBAL-H, THF, −78 °C; iii, PIFA, TEMPO, MeCN–$H_2O$ (4:1), 0 °C [(6′*R*)-**47**, 18% over 2 steps; (6′*S*)-**47**, 23% over 2 steps]; iv, 30% $H_2O_2$, LiOH, Pr$^i$OH, 0 °C [(6′*R*)-**1**, 33%, (6′*S*)-**1**, 22%]

encountered when the deprotection–acylation of the corresponding acetals **37** was investigated. Thus, this convergent approach was reluctantly abandoned in favour of the more linear synthesis in which the acyl side chain was present from the outset. In order to carry out this investigation the aranorosin side chain acid **4** was required in enantiodefined form.

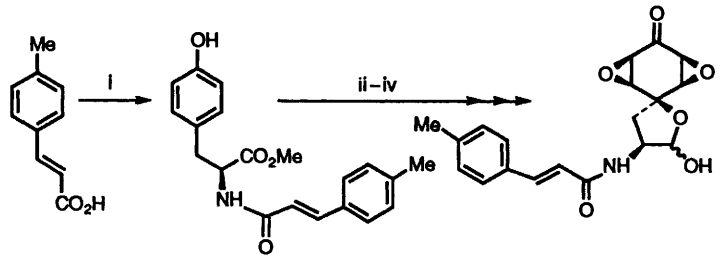
### Preparation of the side chain acids 4

As the 6′-configuration of the side chain had not been elucidated, both enantiomers were required in order to determine which was present in natural aranorosin. Evans' oxazolidinone methodology[23,24] was chosen to achieve this aim as shown in Scheme 6. Thus, (*R*)-4-phenyloxazolidinone **38**[25,26] was acylated with butyllithium–octanoyl chloride and the resulting imide **39** methylated with sodium hexamethyldisilazide (NaHMDS)–methyl iodide. High yields of the methylated products were reproducibly obtained provided the methyl iodide was first passed through neutral alumina.[24] The diastereoisomeric alkylation products **40** and **41** were easily separated by chromatography, **41** being obtained in 84% isolated yield as needles (mp 45–47 °C, $[\alpha]_D$ −93). Reduction of **41** using lithium borohydride in wet diethyl ether[27] gave alcohol **42** in excellent yield. Swern oxidation, Wittig chain extension, DIBAL-H reduction to the allylic alcohol, oxidation with $MnO_2$, a second Wittig reaction and saponification gave the acid **4*R*** in 40% overall yield from **38**. In an analogous manner (*S*)-4-benzyloxazolidinone **43**[23,26] was converted into the enantiomeric acid **4*S*** in 33% overall yield. The optical rotations indicated that the two compounds were indeed enantiomeric {**4*R***, $[\alpha]_D$ −62.5 (*c* 0.54, $CH_2Cl_2$); **4*S***, $[\alpha]_D$ +62.6 (*c* 0.54, $CH_2Cl_2$)}. These values are also in good agreement with those published by Wipf *et al.*[9]

### Synthesis of 6-epiaranorosin, aranorosin and novel aranorosin analogues

The chemistry shown in Scheme 7 was initially carried out using racemic side chain **4**. Amide formation between **4** and tyrosine ethyl ester hydrochloride **44** using either ethyl chloroformate[16] or diphenylphosphinic chloride[28] gave amide **45**. The latter procedure was preferred as the mixed anhydride method gave significant amounts of the ethyl carbamate as a byproduct. DIBAL-H reduction at −78 °C then gave aldehyde **46**. In order to optimise conditions for the PIFA reaction, aldehyde **46** was chromatographed to obtain a colourless foam in 80% yield. Exposure of chromatographically pure **46** to PIFA in wet acetonitrile initially gave an extremely messy reaction. Repeated chromatography on silica eventually gave the desired, but racemic, dienone **47** as a colourless foam in 13% yield as a 3:1 mixture of lactol isomers which was characterised by $^1H$ and $^{13}C$ NMR spectroscopy and HRMS. Several experiments were carried out in attempts to improve the chemical yield of the reaction, including varying the oxidant, temperature and duration of the oxidation, but with little success. We then turned to the use of the stable free radical, 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO), in order to inhibit unwanted side reactions. By addition of 0.5 equivalents of TEMPO and quenching of the oxidation after 2.5 min by addition saturated aqueous sodium bicarbonate, we were able to achieve a yield of 39% of **47** using chromatographically purified aldehyde. Epoxidation was initially carried out using the standard conditions of sodium hydroxide in methanol, but a large number of products were observed in addition to the required product (estimated yield 10%) and optimisation was required. Changing the base to lithium hydroxide gave an improvement in yield to 22%. Also isolated was a byproduct which, while not fully characterised, appeared to result from conjugate addition of methoxide to dienone **47**. The methanolic solvent was therefore replaced by propan-2-ol and this reduced the number of byproducts and improved the yield of **1** to approximately 35%.

This procedure was then repeated using the enantiopure acids **4*R*** and **4*S***. These were separately coupled to tyrosine ethyl ester hydrochloride **44** giving (6′*R*)-**45** and (6′*S*)-**45** in 73 and 81%




**Scheme 8** *Reagents and conditions:* i, TyrOMe·HCl, $Ph_2POCl$, $Et_3N$, THF, rt (67%); ii, DIBAL-H, THF, −78 °C; iii, PIFA, TEMPO, MeCN–$H_2O$ (4:1), 0 °C (19% over 2 steps); iv, 30% $H_2O_2$, LiOH, $Pr^iOH$, 0 °C (27%)

yields, respectively. In order to preserve the optical integrity at the α centre of the tyrosinals **46**, the optimised oxidation conditions (PIFA, TEMPO, aq. MeCN) were employed with freshly prepared, non-chromatographed material and the dienones (6′*R*)-**47** and (6′*S*)-**47** were obtained in 18 and 23% overall yield, respectively for the two steps {6′*R*-, $[\alpha]_D$ −10 (*c* 0.75, $CH_2Cl_2$); 6′*S*-, $[\alpha]_D$ +60.7 (*c* 3.16, $CHCl_3$)}. Epoxidation using LiOH, $H_2O_2$, $Pr^iOH$ then produced (6′*R*)-**1** in 33% yield and (6′*S*)-**1** in 22% yield, both as colourless, crystalline solids and as a 3:1 mixture of lactol anomers according to NMR spectroscopy. The $^1H$ and $^{13}C$ NMR spectroscopic data were similar to those reported for the natural product,[1] and obtained for racemic material, and the melting points for both (6′*R*)-**1** and (6′*S*)-**1**, 150 °C, were in agreement with the published value. The allocation of the structure of the natural product therefore rested on the polarimetric measurements. The diastereoisomer (6′*R*)-**1** gave $[\alpha]_D$ −8.2 (*c* 0.48, $CHCl_3$), whereas the epimeric (6′*S*)-**1** gave $[\alpha]_D$ +33.5 (*c* 0.31, $CHCl_3$). The reported rotation for natural aranorosin was −2.42 (*c* 2.58, $CHCl_3$). While the figures for natural and synthetic compounds were not in exact agreement, these data indicated that natural aranorosin had the 6′*R* configuration. [The optical rotation of synthetic (6′*R*)-**1** was re-measured after storage for 2 weeks, giving $[\alpha]_D$ −3 (*c* 0.5, $CHCl_3$), almost identical to the literature value.] Subsequently, Wipf, Kim and Fritch reported that the optical rotation of a *freshly purified sample* of natural aranorosin was −7.8 (*c* 0.17, $CHCl_3$),[9] in close agreement with the value we obtained for (6′*R*)-**1**, thereby confirming the absolute structure.

The synthesis of aranorosin shown in Scheme 7 is extremely short and well suited to the preparation of analogues. To illustrate this point, the novel aranorosin analogue **49** was prepared as shown in Scheme 8. This research has therefore confirmed the structure of the natural product and resulted in the development of a synthetic route which can be employed to prepare novel analogues. In addition, the stereocontrolled procedures for the preparation of diepoxycyclohexanones developed in this study should be of value for the preparation of the diepoxin natural products.[10] This work is currently in progress.

## Experimental

$^1H$ NMR spectra ($\delta_H$) were recorded using JEOL PMX 60, JEOL EX 270 and JEOL GSX 400 NMR spectrometers, with referencing to $Me_4Si$ as internal standard or to the deuteriochloroform lock, and were assigned using homonuclear decoupling experiments or COSY-45 at 270 or 400 MHz and DIFNOE experiments at 270 MHz where necessary. $^{13}C$ NMR spectra ($\delta_C$) were recorded using JEOL EX 90, JEOL EX 270 or JEOL GSX 400 NMR spectrometers at 22.5, 67.5 or 100 MHz respectively with referencing to the deuteriochloroform lock and were assigned using DEPT or heteronuclear correlation experiments. Samples were run as solutions in $CDCl_3$ unless otherwise stated. *J* Values are quoted in hertz. IR spectra were recorded on a Perkin-Elmer FTIR 1720X spectrometer or an ATI Mattson Genesis Series FTIR and were run as neat films unless otherwise stated. Mass spectra were recorded on a Kratos MS25 (low resolution EI only) or a Fisons Instruments VG Analytical Autospec Spectrometer system (low and high resolution EI and CI spectra). Light petroleum refers to the fraction of boiling range 40–60 °C and was redistilled before use. Tetrahydrofuran (THF) and diethyl ether were dried over sodium–benzophenone ketyl and distilled immediately before use; triethylamine, acetonitrile, dichloromethane and dichloroethane were dried by boiling over calcium hydride and were distilled immediately before use. 'Ether' refers to diethyl ether. Ethyl acetate refers to HPLC grade solvent and was used as purchased. Solutions of organolithium compounds were regularly titrated using diphenylacetic acid.[29] Other starting materials were used as purchased or prepared according to established literature procedures using references given in the text. A standard work-up refers to 2–3 extractions with the specified solvent, washing of the combined extracts with water, drying ($MgSO_4$) and removal of the solvent on a rotary evaporator. Analytical TLC was performed on Merck 5554 aluminium-backed silica gel plates which were visualised using UV, $KMnO_4$–acetone solutions or acidic ethanolic vanillin solutions. Column chromatography was carried out under flash conditions[30] unless otherwise stated using silica gel (Phase Separations Ltd Sorbsil C60 40–60H or ICN Biomedicals GmbH silica 32–63, 60A) and the specified eluent. Melting points were recorded on a Kofler hot-stage melting point apparatus and are uncorrected. Boiling points refer to oven temperatures (Kugelrohr) or distillation temperatures. Microanalyses were performed at the University of East Anglia.

### 4-[2-(1,3-Dioxolan-2-yl)ethyl]-4-hydroxycyclohexa-2,5-dien-1-one 12

The Grignard reagent **10** [prepared[12] from Mg (0.63 g, 25.9 g atom) and 2-(2-bromoethyl)-1,3-dioxolane (4.3 g, 23.8 mmol) in THF (15 ml)] was added dropwise by syringe to a solution of 4,4-dimethoxycyclohexa-2,5-dien-1-one **8** (2.98 g, 19.3 mmol) in THF (20 ml) at −78 °C under nitrogen and the solution stirred at the same temperature for 30 min before warming to room temperature. Addition of saturated aq. $NH_4Cl$ solution (20 ml) followed by a standard ether work-up gave a brown oil (5.35 g) which was taken up in $CH_2Cl_2$ (30 ml) and silica gel (5 g) and saturated aq. oxalic acid solution (2 ml) added. The mixture was stirred for 30 min then filtered and the solid rinsed with $CH_2Cl_2$ (30 ml). The combined solvents were dried ($MgSO_4$) and evaporated to give a brown oil (4.65 g) which was chromatographed (ether) to give recovered dienone **8** (1.0 g, 34%) and the *title compound* **12** (1.94 g, 48%) as a brown oil; $R_f$ 0.23 (ether); bp 250 °C (0.5 mmHg); $\nu_{max}$(neat) 3400, 2980, 2880, 1670, 1630, 1140, 1030 $cm^{-1}$; $\delta_H$(60 MHz) 1.40–1.95 (4 H, m, $CCH_2CH_2C$), 3.32 (1 H, s, OH), 3.78–3.88 (4 H, m, dioxolane protons), 4.80 (1 H, t, *J* 4, OCHO), 6.08 (2 H, d, *J* 10, 2-H and 6-H), 6.76 (2 H, d, *J* 10, 3-H and 5-H); $\delta_C$(22.4 MHz) 29.7, 33.7, 64.9, 69.1, 103.5, 128.1, 151.2, 185.5; *m*/*z* (EI): 210 ($M^+$, 0.5%) [HRMS (CI): Found: $[M + NH_4]^+$, 228.1240. $C_{11}H_{18}NO_4$ requires 228.1236].

**(1*S**,2*R**,3*R**,5*R**,7*S**)-2-[2-(1,3-Dioxolan-2-yl)ethyl]-2-hydroxy-4,8-dioxatricyclo[5.1.0.0$^{3,5}$]octan-6-one 13**

Sodium hydroxide (6 mol $l^{-1}$; 0.5 ml, 3 mmol) was added dropwise to a stirred mixture of enone **12** (1.16 g, 5.52 mmol) in methanol (4 ml) and 30% aq. hydrogen peroxide (1.7 ml) at 0 °C and the mixture stirred for 3 h. It was then poured into water, and the resulting mixture given a standard ethyl acetate work-up (5 × 50 ml, **CAUTION**: peroxidic by-products may be present[4]). The crude product, obtained as a colourless glass, was redissolved in ethyl acetate (100 ml), activated 4 Å molecular sieves (10 g) added and the mixture stirred for 6 h to destroy any peroxidic byproducts. The solution was decanted, and evaporation of the solvent gave a colourless oil (1.06 g) which was purified by chromatography (EtOAc–$CH_2Cl_2$, 1:1) to give the *title compound* **13** as a colourless solid (0.92 g, 69%), which was recrystallised from EtOAc–hexane, mp 84.5–86.5 °C; $R_f$ 0.52 (EtOAc) (Found: C, 54.62; H, 5.66. $C_{11}H_{14}O_6$ requires C, 54.5; H, 5.8%); $\nu_{max}$(Nujol) 3460, 1710 $cm^{-1}$; $\delta_H$(400 MHz) 1.80–1.96 (4 H, m, $CCH_2CH_2C$), 3.48–3.52 (5 H, m, rem.), 3.86–4.01 (4 H, m, dioxolane protons), 4.93 (1 H, t, *J* 4, OCHO); $\delta_C$(22.4 MHz) 26.9, 29.9, 56.9, 63.8, 65.1, 68.5, 103.3, 198.8; *m/z* (EI) 241 ($M^+$ − H, 0.8%).

**Attempted preparation of 2-hydroxy-6,7,9,10-diepoxy-1-oxaspiro[4.5]decan-8-one 15; isolation of dimer 14**

Bis(acetonitrile)palladium(II) chloride (15 mg, 0.056 mmol) was added to a solution of diepoxide **13** (0.20 g, 0.83 mmol) in dry acetone (10 ml) and the mixture was allowed to stand for 2 h. The solvent was then removed *in vacuo* and the residue chromatographed (EtOAc) to give *dimer* **14** (0.15 g, 86%) as a colourless foam. An analytical sample was prepared by recrystallisation from acetone; mp 207–208 °C; $R_f$ 0.34 (EtOAc) (Found: C, 56.7; H, 5.4. $C_{20}H_{22}O_{10}$ requires C, 56.9; H, 5.25%); $\nu_{max}$(Nujol) 1725, 1708, 1038 $cm^{-1}$; $\delta_H$[400 MHz; $(CD_3)_2CO$] 2.13–2.23 (8 H, m, 2 × $CCH_2CH_2C$), 3.34 (2 H, dd, *J* 4 and 2.5, 2 × 9-H), 3.39 (2 H, dd, *J* 4 and 2.5, 2 × 7-H), 3.53 (2 H, dd, *J* 4 and 3.5, 2 × 10-H), 3.64–3.71 (4 H, m, 2 × 6-H + $OCH_2CH_2O$), 3.91–3.96 (2 H, m, $OCH_2CH_2O$), 5.33 (2 H, appt. t, *J* 2.5, 2 × 2-H); $\delta_C$(100 MHz; $CDCl_3$) 30.2, 32.5, 55.3, 55.5, 62.8, 63.9, 65.9, 79.7, 104.8, 198.9; *m/z* (CI) 440 ($M + NH_4^+$) [HRMS (CI) Found: $M + NH_4^+$, 440.1580. $C_{20}H_{26}NO_{10}$ requires 440.1556].

**2-Hydroxy-6,7,9,10-diepoxy-1-oxaspiro[4.5]decan-8-one 15**

Bis(acetonitrile)palladium(II) chloride (10 mg, 0.039 mmol) was added to a solution of the diepoxide acetal **13** (0.082 g, 0.34 mmol) in acetone (9 ml). Water (1 ml) was added and the mixture was allowed to stand for 3 d in the dark. The solvent was removed *in vacuo* and the residue chromatographed (EtOAc) to give an oil (0.051 g) as a 4:1 mixture of hemiacetal **15** and dimer **14** according to 270 MHz $^1H$ NMR spectroscopy. Rechromatography (EtOAc–$CH_2Cl_2$–MeOH, 10:10:1) gave pure hemiacetal **15** (0.041 g, 61%) as a colourless solid, mp 162–163 °C (lit.,[5] mp 162–163 °C), which gave IR and NMR data identical to those reported.[5]

**(2*E*,4*E*,6*R*)-4,6-Dimethyldodeca-2,4-dienoic acid 4*R***

(*a*) A solution of butyllithium in hexanes (2.32 mol $l^{-1}$; 13.4 ml, 31.1 mmol) was added dropwise over 5 min to a solution of oxazolidinone **38**[25,26] (5.07 g, 31 mmol) in THF (50 ml) at −78 °C under nitrogen and the mixture was stirred for 10 min. Octanoyl chloride (6.3 ml, 6 g, 37 mmol) was added and the solution stirred for 30 min, then warmed to room temperature and quenched with saturated aq. $NH_4Cl$ (30 ml). The solvent was removed *in vacuo*, and the residue was taken up in water (100 ml). A standard $CH_2Cl_2$ work-up gave a colourless solid (10.6 g) which was recrystallised from hexanes to give (R)-3-(1-*oxooctyl*)-4-*phenyl*-1,3-*oxazolidin*-2-*one* **39** (8.45 g, 94%) as colourless needles, mp 39.5–40 °C; $R_f$ 0.18 (ether–hexanes, 5:1); $[\alpha]_D$ +51.4 (*c* 1.04, $CHCl_3$) (Found: C, 70.6; H, 8.0; N, 4.8. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8%); $\nu_{max}$(Nujol) 1790, 1770, 1700, 1090, 1070 $cm^{-1}$; $\delta_H$(270 MHz) 0.86 (3 H, t, *J* 7, Me), 1.18–1.35 (8 H, m, rem.), 1.52–1.64 (2 H, m, 3′-$CH_2$), 2.84–2.98 (2 H, m, 2′-$CH_2$), 4.23 (1 H, dd, *J* 9 and 3.5, 5-H), 4.66 (1 H, appt. t, *J* 9, 5-H), 5.40 (1 H, dd, *J* 9 and 3.5, 4-H), 7.26–7.40 (5 H, m, Ph); $\delta_C$(67.5 MHz) 14.0, 22.2, 22.5, 24.0, 28.9, 31.5, 35.4, 57.5, 69.9, 125.8, 128.5, 129.0, 139.2, 153.6, 172.8; *m/z* (EI) 290 ($M + H^+$, 2%), 289 ($M^+$, 9.8).

(*b*) Sodium hexamethyldisilazide (NaHMDS) in THF (1.0 mol $l^{-1}$; 15 ml, 15 mmol) was added dropwise to a solution of imide **39** (4.0 g, 13.8 mmol) in THF (80 ml) at −78 °C under nitrogen and the solution stirred for 90 min. Methyl iodide (5 ml, 11.4 g, 80 mmol) (freshly passed through a column of active alumina) was added and the solution stirred at −78 °C for 3 h, then quenched with saturated aq. $NH_4Cl$ (50 ml). A standard ether work-up gave the crude product (4.18 g) as an 87:13 mixture of diastereoisomers **41**:**40** as determined by 270 MHz $^1H$ NMR spectroscopy. Chromatography (ether–hexanes, 1:3) gave (2′R,4R)-3-(2-*methyl*-1-*oxooctyl*)-4-*phenyl*-1,3-*oxazolidin*-2-*one* **41** (3.53 g, 84%) as colourless solid, mp 45–47.5 °C; $R_f$ 0.29 (ether–hexanes, 1:3); $[\alpha]_D$ −93 (*c* 0.97, $CHCl_3$) (Found: C, 71.3; H, 8.3; N, 4.8. $C_{18}H_{25}NO_3$ requires C, 71.3; H, 8.3; N, 4.6%); $\nu_{max}$(Nujol) 1785, 1770, 1705, 1210, 1020 $cm^{-1}$; $\delta_H$(270 MHz) 0.80 (3 H, t, *J* 6.5, 8′-Me), 1.03 (3 H, d, *J* 7, 2′-Me), 1.16–1.28 (9 H, m, rem.), 1.59–1.68 (1 H, m, 3′-H), 3.66 (1 H, sextet, *J* 7, 2′-H), 4.16 (1 H, dd, *J* 9 and 3.5, 5-H), 4.60 (1 H, appt. t, *J* 9, 5-H), 5.36 (1 H, dd, *J* 3.5 and 8.5, 4-H), 7.20–7.35 (5 H, m, Ph); $\delta_C$(67.5 MHz) 14.0, 17.2, 22.5, 27.2, 29.2, 31.6, 33.0, 37.7, 57.6, 69.7, 125.6, 128.5, 129.1, 139.3, 153.3, 176.6; *m/z* (EI) 303 ($M^+$, 2.8%).

(*c*) Lithium borohydride (0.17 g, 7.8 mmol) was added to a solution of imide **41** (2.34 g, 7.71 mmol) in ether (50 ml) and water (0.15 g) at 0 °C and the solution was stirred for 60 min. Sodium hydroxide solution (1 mol $l^{-1}$; 50 ml) was added and the mixture stirred until both phases were clear. The organic solvent was separated, dried ($MgSO_4$) and evaporated, the solid residue was triturated with hexanes and recovered oxazolidinone **38** was collected by filtration. Evaporation of the filtrate gave (R)-2-*methyloctanol* **42*R***[9] (0.98 g, 88%) as a colourless liquid; $R_f$ 0.55 (ether–hexanes, 1:1); $[\alpha]_D$ +10.3 (*c* 1.0, $CH_2Cl_2$) (Found: C, 74.8; H, 14.15. $C_9H_{20}O$ requires C, 74.9; H, 14.0%); $\nu_{max}$(neat) 3350, 2980, 1030 $cm^{-1}$; $\delta_H$(270 MHz) 0.86 (3 H, t, *J* 7, 8-Me), 0.88 (3 H, d, *J* 7, 2-Me), 1.04–1.14 (1 H, m, 7-$CH_2$), 1.20–1.40 (8 H, m, rem.), 1.45 (1 H, br s, OH), 1.54–1.61 (1 H, m, 2-H), 3.38 (1 H, dd, *J* 6.5 and 10.5, 1-H), 3.48 (1 H, dd, *J* 6.5 and 10.5, 1-H); $\delta_C$(67.5 MHz) 14.0, 16.5, 22.6, 26.9, 29.6, 31.8, 33.1, 35.7, 68.3; *m/z* (EI) 127 ($M^+ + 1 - H_2O$, 2%), 126 ($M^+ - H_2O$, 13).

(*d*) DMSO (2.71 ml, 3.22 g, 38 mmol) was added dropwise to a solution of oxalyl chloride (2.42 g, 19 mmol) in $CH_2Cl_2$ (15 ml) at −78 °C under nitrogen and the resulting mixture was stirred for 30 min at the same temperature. Alcohol **42** (0.986 g, 6.84 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise and the resulting solution was stirred for 30 min. Triethylamine (6.5 ml, 4.72 g, 47 mmol) was added dropwise and the mixture was stirred for 45 min, with warming to 0 °C. The suspension was poured into water (50 ml) and the mixture was extracted with ether (2 × 50 ml). The organic extracts were washed with potassium hydrogen sulfate (10% aq., 40 ml), saturated aq. sodium hydrogen carbonate (50 ml) and brine (50 ml), then dried ($MgSO_4$) and evaporated to give the (*R*)-2-methyloctanal[9] (*ca.* 1.00 g, 100%) as a pale yellow liquid which was used immediately in the next step.

(*e*) (1-Ethoxycarbonylethylidene)triphenylphosphorane (5.0 g, 13.8 mmol) was added to a solution of 2-methyloctanal (0.98 g, 6.9 mmol) in toluene (50 ml) under nitrogen. The mixture was boiled under reflux for 3 h, then cooled to room temperature, filtered through silica (20 g, ether), evaporated and chromatographed (ether–hexanes, 1:10) to give ethyl (2*E*,4*R*)-2,4-dimethyldec-2-enoate[9] (1.31 g, 84%) as a colourless

liquid; $R_f$ 0.37 (ether–hexanes, 1:10); $[\alpha]_D$ −25.9 (*c* 0.75, $CH_2Cl_2$) (Found: C, 74.2; H, 11.4. $C_{14}H_{26}O_2$ requires C, 74.3; H, 11.6%); $\nu_{max}$(neat) 2860, 1715, 1650, 1460, 1280, 1248, 1190, 1140, 1100 $cm^{-1}$; $\delta_H$(270 MHz) 0.82 (3 H, t, *J* 6, 10-Me), 0.96 (3 H, d, *J* 6.5, 4-Me), 1.13–1.40 (10 H, m, rem.), 1.27 (3 H, t, *J* 7, $OCH_2CH_3$), 1.80 (3 H, d, *J* 1.5, 2-Me), 2.38–2.47 (1 H, m, 4-H), 4.13 (2 H, q, *J* 7, $OCH_2CH_3$), 6.50 (1 H, dq, *J* 10 and 1.5, 3-H); $\delta_C$(67.5 MHz) 12.5, 14.0, 14.3, 20.0, 22.6, 27.4, 29.4, 31.8, 33.2, 36.9, 60.3, 126.3, 148.1, 168.5.

(*f*) A solution of diisobutylaluminium hydride (DIBAL-H) (1 mol $l^{-1}$ in hexanes; 10 ml, 10 mmol) was added dropwise over 5 min to a solution of the above ester (0.98 g, 4.33 mmol) in THF (20 ml) at −78 °C, and the mixture was stirred for 3 h, then warmed to −20 °C. Methanol (5 ml) was added cautiously, then the solution was poured into sodium tartrate (20% aq., 40 ml) and the resulting mixture was stirred vigorously for 1 h. An ether work-up (2 × 30 ml), incorporating a brine (30 ml) wash, followed by chromatography (ether–hexanes, 1:8) of the residue gave the (2*E*,4*R*)-2,4-dimethyldec-2-en-1-ol[9] (0.78 g, 98%) as a colourless liquid; $R_f$ 0.63 (ether–hexanes, 1:4); $[\alpha]_D$ −10.5 (*c* 2.1, $CH_2Cl_2$); $\nu_{max}$(neat) 3320, 1460, 1380, 1070, 1010 $cm^{-1}$; $\delta_H$(270 MHz) 0.85 (3 H, t, *J* 6.5, 10-Me), 0.90 (3 H, d, *J* 7, 4-Me), 1.14–1.34 (10 H, m, rem.), 1.64 (3 H, d, *J* 1.5, 2-Me), 2.32–2.38 (1 H, m, 4-H), 3.97 (2 H, s, 1-H), 5.14 (1 H, dq, *J* 9.5 and 1.5, 3-H); $\delta_C$(67.5 MHz) 13.8, 14.0, 20.9, 22.7, 27.4, 29.5, 31.6, 31.9, 37.6, 69.1, 133.1 (2C).

(*g*) A solution of the above allylic alcohol (0.78 g, 4.23 mmol) in $CH_2Cl_2$ (40 ml) was boiled under reflux with manganese dioxide (5.5 g, 63 mmol) for 2 h. TLC showed clean conversion to a single product at $R_f$ 0.50 (ether–hexanes, 1:4). The suspension was filtered and the filtrate evaporated to give (2*E*,4*R*)-2,4-dimethyldec-2-enal[9] (0.77 g, 100%) as a colourless liquid which was used immediately in the next step.

(*h*) A solution of the above aldehyde (0.77 g, 4.2 mmol) and (ethoxycarbonylmethylidene)triphenylphosphorane (2.94 g, 8.44 mmol) was boiled under reflux in toluene (40 ml) for 3 h. Further phosphorane (0.5 g) was added and the reaction continued for 30 min. Methanol (5 ml) was added, then the solvent removed *in vacuo* and the residue chromatographed (ether–hexanes, 1:4) to give ethyl (2*E*,4*E*,6*R*)-4,6-dimethyldodeca-2,4-dienoate[9] (0.93 g, 87%) as a colourless liquid; $R_f$ 0.29 (ether–hexanes, 1:10); $[\alpha]_D$ −33 (*c* 1.04, $CH_2Cl_2$); $\nu_{max}$(neat) 1720, 1630, 1460, 1300, 1170, 1030 $cm^{-1}$; $\delta_H$(270 MHz) 0.80 (3 H, t, *J* 7, 12-Me), 0.91 (3 H, d, *J* 6.5, 6-Me), 1.10–1.28 (10 H, m, rem.), 1.23 (3 H, t, *J* 7, $OCH_2CH_3$), 1.70 (3 H, d, *J* 1, 4-Me), 2.38–2.47 (1 H, m, 6-H), 4.14 (2 H, q, *J* 7, $OCH_2CH_3$), 5.60 (1 H, d, *J* 10, 5-H), 5.70 (1 H, d, *J* 16 Hz, 2-H), 7.24 (1 H, dd, *J* 1 and 16, 3-H); $\delta_C$(67.5 MHz) 12.3, 14.0, 14.3, 20.5, 22.6, 27.4, 29.4, 31.8, 33.2, 60.1, 115.5, 131.2, 148.7, 149.9, 167.6; *m/z* (EI) 252 ($M^+$, 4%).

(*i*) Lithium hydroxide (0.7 g, 29 mmol) in water (4 ml) was added to a solution of the above ester (0.83 g, 3.3 mmol) in THF (7 ml) and methanol (4 ml) and the mixture was stirred for 12 h at room temperature. The pH was adjusted to 1.5 by addition of 10% aq. HCl and the cloudy solution extracted with ether (2 × 30 ml) to give, after drying ($MgSO_4$) and evaporation, the title compound **4*R*** (0.60 g, 81%) as pale yellow oil, $[\alpha]_D$ −57.6 (*c* 0.51, $CH_2Cl_2$). A sample was purified by extraction into sodium hydroxide (1 mol $l^{-1}$; 20 ml), acidification with hydrochloric acid (1 mol $l^{-1}$ aq.) and extraction with ether. Drying ($MgSO_4$) and evaporation of the solvent gave pure acid **4*R*** $[\alpha]_D$ −62.5 (*c* 0.54, $CH_2Cl_2$) [lit.,[9] −63.9 (*c* 2.1, $CH_2Cl_2$)] (Found: C, 75.0; H, 11.0. Calc. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.8%) which gave identical IR and NMR spectral data to those reported.[9]

**(2*E*,4*E*,6*R*)-4,6-Dimethyldodeca-2,4-dienoic acid 4*S***

Following the procedures described above,[9] oxazolidinone **43**[23,26] was converted into the title compound in 33% overall yield (step *a*, 97%; step *b* 82%; step *c*, 97%; step *d*, 100%; step *e*, 82%; step *f*, 93%; step *g*, 100%; step *h*, 69%; step *i*, 80%); $[\alpha]_D$ +62.6 (*c* 0.54, $CH_2Cl_2$) [lit.,[9] +63.3 (*c* 1.0, $CH_2Cl_2$)] (Found: C, 74.7; H, 10.9. Calc. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.8%) which gave identical spectral data to those reported.[9]

**Ethyl (2*S*,2′*E*,4′*E*,6′*R*)-2-(4,6-dimethyldodeca-2,4-dienoylamido)-3-(4-hydroxyphenyl)propanoate 45*R***

Diphenylphosphinic chloride (0.66 g, 2.8 mmol) was added to a solution of acid **4*R*** (0.50 g, 2.23 mmol) and triethylamine (0.68 g, 6.7 mmol) in THF (40 ml) at room temperature and the mixture was stirred for 30 min under nitrogen. Tyrosine ethyl ester hydrochloride **44** (0.66 g, 2.69 mmol) was added and the suspension stirred for 6 h at room temperature. An ether work-up (3 × 50 ml) followed by washing with water (30 ml) and brine (50 ml), drying ($MgSO_4$) and evaporation gave a viscous oil which was chromatographed (ether–hexanes, 3:2 + 1% AcOH) to give the *title compound* **45*R*** (0.687 g, 73%) as a colourless viscous oil; $R_f$ 0.63 (ether); $[\alpha]_D$ +107 (*c* 1.76, $CDCl_3$); $\nu_{max}$($CHCl_3$) 3598, 3425, 3250, 2960, 1734, 1658, 1614, 1515, 1446, 1396, 1352, 1303, 1200, 1114, 1025, 981, 930 $cm^{-1}$; $\delta_H$(270 MHz) 0.85 (3 H, t, *J* 6.5, 12′-Me), 0.93 (3 H, d, *J* 6.5, 6′-Me), 1.16–1.29 (10 H, m, rem.), 1.24 (3 H, t, *J* 7, $OCH_2CH_3$), 1.72 (3 H, d, *J* 0.5, 4′-Me), 2.40–2.55 (1 H, m, 6′-H), 3.00–3.14 (2 H, m, 3-$CH_2$), 4.16 (2 H, q, *J* 7, $OCH_2CH_3$), 4.89–4.96 (1 H, m, 2-H), 5.61 (1 H, d, *J* 9.5, 5′-H), 5.72 (1 H, d, *J* 15.5, 2′-H), 6.03 (1 H, d, *J* 8, NH), 6.33 (1 H, br s, OH), 6.71 (2 H, d, *J* 8.5, ArH), 6.94 (2 H, d, *J* 8.5, ArH), 7.21 (1 H, d, *J* 15.5, 3′-H); $\delta_C$(67.5 MHz) 12.5, 14.0, 14.1, 20.5, 22.6, 27.4, 29.4, 31.8, 33.2, 37.2, 37.3, 53.5, 61.6, 115.5, 116.9, 127.2, 130.3, 130.8, 147.4, 148.3, 155.4, 166.5, 172.0; *m/z* (EI) 416 (*M* + 1, 1.6%), 415 ($M^+$, 5.3) [HRMS Found: $MH^+$, 416.2801. $C_{25}H_{38}NO_4$ requires 416.2801].

**(2*R*′/*S*,3*S*,2′*E*,4′*E*,6′*R*)-2-Hydroxy-3-(4,6-dimethyldodeca-2,4-dienoylamido)-1-oxaspiro[4.5]deca-6,9-dien-8-one 47*R***

(*a*) A solution of DIBAL-H in heptane (1.0 mol $l^{-1}$; 7 ml, 7 mmol) was added dropwise to a solution of ester **45*R*** (0.655 g, 1.58 mmol) in THF (50 ml) at −78 °C and the mixture was stirred for 3 h. Methanol (3 ml) was added and the solution was then poured into 20% aq. sodium tartrate (30 ml). The biphasic mixture was stirred at 0 °C for 2 h, then a standard ether work-up (3 × 50 ml) incorporating a brine wash gave aldehyde **46*R*** (0.57 g, 97%) as a colourless foam which was used immediately.

(*b*) Iodobenzene bis(trifluoroacetate) (PIFA) (0.45 g, 1.05 mmol) was added to a vigorously stirred solution of crude aldehyde **46*R*** (0.417 g, 1.12 mmol) and 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) (0.078 g, 0.5 mmol) in MeCN (30 ml) and water (6 ml) at 0 °C. After 2 min, saturated aq. sodium hydrogen carbonate (20 ml) was added and an ether work-up (3 × 50 ml) incorporating a brine (50 ml) wash gave a yellow oil. Chromatography (ether–hexanes, 10:1) gave the *title compound* **47*R*** (0.078 g, 18%) as a pale yellow foam; $R_f$ 0.25 (ether–hexanes, 10:1); $[\alpha]_D$ −10.0 (*c* 0.75, $CH_2Cl_2$); $\nu_{max}$($CDCl_3$) 3690, 3605, 3434, 3300, 2960, 2855, 1672, 1634, 1613, 1507, 1453, 1395, 1300, 1261, 1177, 1116, 1074, 1026, 981, 931 $cm^{-1}$; $\delta_H$(270 MHz) 0.76 (3 H, t, *J* 6.5, 12′-Me), 0.90 (3 H, d, *J* 6.5, 6′-Me), 1.16–1.26 (10 H, m, rem.), 1.74 (3 H, d, *J* 1, 4′-Me), 2.12 (1 H, dd, *J* 11 and 13, 4-H), 2.42–2.53 (1 H, m, 6′-H), 2.46 (1 H, dd, *J* 8.5 and 13, 4-H), 3.83 (1 H, br s, OH), 4.75–4.86 (1 H, m, 3-H), 5.51 (1 H, d, *J* 4.5, 2-H), 5.64 (1 H, d, *J* 9.5, 5′-H), 5.73 (1 H, d, *J*, 2′-H), 5.96 (1 H, d, *J* 8.5, NH), 6.12 (2 H, d, *J* 10, 7-H, 9-H), 6.79–6.91 (2 H, m, 6-H, 10-H), 7.24 (1 H, d, *J* 15, 3′-H); $\delta_C$(67.5 MHz) 12.5, 14.0, 20.5, 22.6, 27.4, 29.4, 31.8, 33.2, 37.2, 38.7, 52.5, 77.3, 96.4, 117.0, 127.3, 130.8, 147.4, 148.4, 148.5, 151.0, 166.8, 185.3 [HRMS Found: $MH^+$, 388.2488. $C_{23}H_{34}NO_4$ requires 388.2488].

**Aranorosin (6*R*)-1**

To a solution of dienone **47*R*** (0.075 g, 0.194 mmol) in propan-2-ol (3 ml) was added 30% hydrogen peroxide (0.20 ml, 1.7 mmol) followed by aq. lithium hydroxide (1 mol $l^{-1}$; 0.4 ml, 0.4

mmol) at 0 °C and the mixture was stirred at the same temperature for 2 h, then poured into brine (5 ml). A standard ethyl acetate work-up gave a colourless oil which was chromatographed ($CH_2Cl_2$–EtOAc, 7:3 + 1% MeOH) to give a colourless solid (0.0389 g, 47%). This was rechromatographed ($CH_2Cl_2$–MeOH, 95:5) to give the *title compound* (6′*R*)-**1** (0.0267 g, 33%) as a colourless solid, mp 150 °C (decomp.) [lit.,[1] mp 150 °C (decomp.)]; $R_f$ 0.49 ($CHCl_3$–MeOH, 85:15); $[\alpha]_D$ −8.2 (*c* 0.48, $CHCl_3$) {lit.,[1] $[\alpha]_D$ −2.42 (*c* 2.58, $CHCl_3$); lit.,[9] $[\alpha]_D$ −7.8 (*c* 0.17, $CHCl_3$)}; $\nu_{max}(CDCl_3)$ 3680, 3600, 3431, 2959, 2855, 1726, 1662, 1616, 1507, 1456, 1265, 1046, 982, 932, 885, 764 $cm^{-1}$; $\delta_H$(270 MHz) 0.85 (3 H, t, *J* 6.5, 12′-Me), 0.95 (3 H, d, *J* 6.5, 6′-Me), 1.15–1.26 (10 H, m, rem.), 1.75 (3 H, d, *J* 1, 4′-Me), 2.01 (1 H, dd, *J* 10.5 and 13, 4-H), 2.40–2.55 (1 H, m, 6′-H), 2.58 (1 H, dd, *J* 8.5 and 13, 4-H), 3.40–3.46 (2 H, m, 7-H, 9-H), 3.54 (1 H, dd, *J* 3.5 and 4.1, 10-H), 3.66 (1 H, dd, *J* 3 and 3.5, 6-H), 4.21 (1 H, br s, OH), 4.70–4.84 (1 H, m, 3-H), 5.62 (1 H, d, *J* 4.5, 2-H), 5.65 (1 H, d, *J* 10, 5′-H), 5.74 (1 H, d, *J* 15, 2′-H), 6.06 (1 H, d, *J* 8.5, NH), 7.24 (1 H, d, *J* 15, 3′-H); $\delta_C$(67.5 MHz) 12.5, 14.0, 20.5, 22.6, 27.4, 29.4, 31.8, 33.2, 35.9, 37.2, 52.0, 55.6, 55.9, 62.9, 64.3, 78.7, 96.5, 116.9, 130.8, 147.4, 148.5, 166.9, 198.4 [HRMS Found: $MH^+ - H_2O$, 402.2280. Calc. for $C_{23}H_{32}NO_5$ 402.2280].

**6′-Epiaranorosin (6′*S*)-1**

The title compound was prepared following similar procedures to those used to prepare aranorosin (6′*R*)-**1** from acid **4*R***. The IR and NMR data for the intermediates was essentially the same as for the (6′*R*)-series.

(*a*) Acid **4*S*** (1.05 g, 4.68 mmol) and tyrosine ethyl ester hydrochloride **44** (1.38 g, 5.62 mmol) gave *ethyl* (2S,2′E,4′E,6′S)-2-(4,6-*dimethyldodeca*-2,4-*dienoylamido*)-3-(4-*hydroxyphenyl*)*propanoate* **45*S*** (1.57 g, 81%) as a colourless viscous oil; $R_f$ 0.63 (ether); $[\alpha]_D$ +161 (*c* 3.3, $CDCl_3$) (Found: C, 71.9; H, 8.9; N, 3.3. $C_{25}H_{37}NO_4$ requires C, 72.3; H, 9.0; N, 3.4%).

(*b*) Ester **45*S*** (1.47 g, 3.54 mmol) and DIBAL-H (1 mol $l^{-1}$ in heptane; 14 ml, 14 mmol) gave the aldehyde **46*S*** which was oxidised with PIFA (1.39 g, 3.2 mmol) to (3*S*,2′*E*,4′*E*,6′*S*)-2-hydroxy-3-(4,6-dimethyldodeca-2,4-dienoylamido)-1-oxaspiro-[4.5]deca-6,9-dien-8-one **47*S*** (0.32 g, 23%), which was obtained as a pale yellow foam; $[\alpha]_D$ +60.7 (*c* 3.16, $CHCl_3$).

(*c*) Dienone **47*S*** (0.25 g, 0.65 mmol), 30% hydrogen peroxide (0.7 ml, 6 mmol) and aq. lithium hydroxide (1 mol $l^{-1}$; 0.2 ml, 0.2 mmol) gave the *title compound* (6′*S*)-**1** (0.060 g, 22%) as colourless solid, mp 150 °C (decomp.); $R_f$ 0.50 ($CHCl_3$–MeOH, 85:15); $[\alpha]_D$ +33.5 (*c* 0.31, $CHCl_3$); $\nu_{max}(CDCl_3)$ 3690, 3600, 3430, 2960, 2928, 2856, 1725, 1704, 1657, 1613, 1510, 1456, 1395, 1262, 1200, 1101, 1026, 983, 932 $cm^{-1}$; $\delta_H$(270 MHz) 0.85 (3 H, t, *J* 7, 12′-Me), 0.95 (3 H, d, *J* 7, 6′-Me), 1.14–1.36 (10 H, m, rem.), 1.75 (3 H, d, *J* 1, 4′-Me), 2.01 (1 H, dd, *J* 10.5 and 13, 4-H), 2.42–2.54 (1 H, m, 6′-H), 2.57 (1 H, dd, *J* 8.5 and 13, 4-H), 3.41–3.46 (2 H, m, 7-H, 9-H), 3.53 (1 H, appt. t, *J* 3.5, 10-H), 3.64 (1 H, dd, *J* 3.5 and 4, 6-H), 3.89 (1 H, br s, OH), 4.75–4.82 (1 H, m, 3-H), 5.60 (1 H, d, *J* 4.5, 2-H), 5.64 (1 H, d, *J* 10.5, 5′-H), 5.74 (1 H, d, *J* 16, 2′-H), 6.02 (1 H, d, *J* 8, NH), 7.23 (1 H, d, *J* 16, 3-H); $\delta_C$(67.5 MHz) 12.5, 14.1, 20.5, 22.6, 27.4, 29.4, 31.8, 33.2, 35.8, 37.1, 52.0, 55.6, 55.8, 62.9, 64.3, 78.7, 96.5, 116.0, 130.8, 147.4, 148.5, 166.9, 198.4 [HRMS Found: $MH^+$, 420.2386. $C_{23}H_{34}NO_6$ requires 420.2386].

**(2*R*/*S*,3*S*,5*S*,6*S*,7*R*,9*S*,10*R*,10*R*,2′*E*)-2-Hydroxy-3-[3′-(4″-methylphenyl)propenoylamido]-6,7,9,10-diepoxy-1-oxaspiro-[4.5]decan-8-one 49**

Following the procedures described above (see Scheme 8), 3-(4-methylphenyl)propenoic acid was converted into the *title compound* **49** (0.105 g, 27%) which was obtained as a white solid, mp 162 °C (decomp.); $R_f$ 0.18 ($CH_2Cl_2$–MeOH, 95:5); $[\alpha]_D$ −25.5 (*c* 0.98, MeOH); $\nu_{max}$(Nujol) 3300, 2950, 1704, 1657, 1607, 1530, 1456, 1377, 1105, 1020 $cm^{-1}$; $\delta_H$[270 MHz; $(CD_3)_2CO$] 2.15 (1 H, dd, *J* 13 and 11, 4-H), 2.33 (3 H, s, ArMe), 2.57 (1 H, dd, *J* 8.5 and 13, 4-H), 3.34–3.39 (2 H, m, 7-H, 9-H), 3.66 (1 H, appt. t, *J* 3.5, 6-H), 3.70 (1 H, dd, *J* 4 and 3.5, 10-H), 4.62–4.75 (1 H, m, 3-H), 5.54 (1 H, dd, *J* 3.5 and 4, 2-H), 6.30 (1 H, d, *J* 3.5, OH), 6.79 (1 H, d, *J* 16, 2′-H), 7.19–7.23 (2 H, m, Ar-H), 7.42–7.49 (3 H, m, Ar-H and NH), 7.52 (1 H, d, *J* 16, 3′-H); $\delta_C$[67.5 MHz; $(CD_3)_2CO$] 21.3, 36.1, 52.9, 55.9, 56.0, 63.7, 65.1, 79.0, 97.3, 121.4, 128.5, 128.5, 130.3, 133.4, 140.8, 166.2, 200.0 [HRMS Found: $MH^+$, 358.1290. $C_{19}H_{20}NO_6$ requires 358.1291].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