

Enantioselective total synthesis of vicenistatin, a novel 20-membered macrocyclic lactam antitumor antibiotic

Yoshitaka Matsushima,^a Hiroaki Itoh,^a Takuya Nakayama,^a Sayo Horiuchi,^a Tadashi Eguchi^b and Katsumi Kakinuma^{*a}

^a Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

^b Department of Chemistry and Materials Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received (in Cambridge, UK) 6th December 2001, Accepted 12th February 2002

First published as an Advance Article on the web 4th March 2002

Enantioselective total synthesis of an antitumor antibiotic, vicenistatin, featuring a 20-membered macrocyclic lactam glycoside with the amino sugar vicenisamine, has been achieved. Key reactions in the synthesis of macrolactam aglycone involved Suzuki cross-coupling and Evans asymmetric aldol reaction. Penultimate glycosidation of the *O*-TMS-aglycone with appropriately protected 1-*O*-acetyl amino sugar and final deprotection allowed accomplishment of the total synthesis.

Vicenistatin (**1**), an antitumor antibiotic isolated from *Streptomyces* sp. HC-34, is interesting because of its novel structural features, including a 20-membered macrocyclic lactam aglycone and a new amino sugar (vicenisamine) as shown in Fig. 1.¹

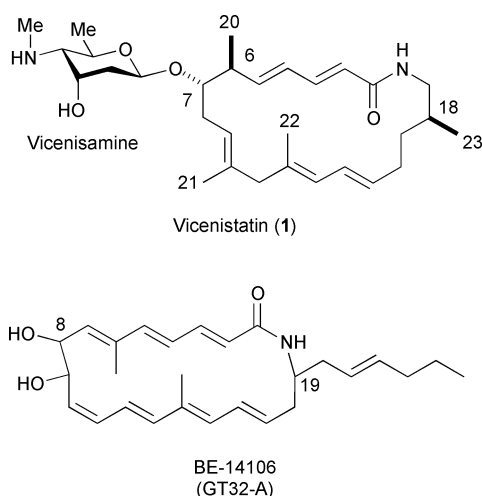


Fig. 1 Structures of vicenistatin and BE-14106 (GT-32A).

A major biological characteristic is its significant inhibitory activity, especially against HL-60 (human leukaemia) and COLO205 (human colon carcinoma) *in vitro* and Co-3 (human colon carcinoma) *in vivo*.¹ The structure shown was determined mainly by extensive NMR spectral analysis¹ and the absolute stereochemistry of the aglycone part was determined by the synthetic approach.² So far, several kinds of macrocyclic lactam antibiotics have been reported including ansamycin antibiotics, hitachimycin³ (strobomycin⁴) and BE-14106⁵ (GT32-A⁶). In particular, BE-14106 should be noted here because of its 20-membered macrocyclic lactam structure. However, vicenistatin is distinct from those antibiotics by containing an amino sugar and by exhibiting intriguing antitumor activities. Recently, we have reported vicenistatin M, a neutral congener having D-mycarose instead of vicenisamine, and have determined its absolute structure by synthesis from synthetic D-mycarose and the naturally derived aglycone.⁷ Interestingly, vicenistatin M

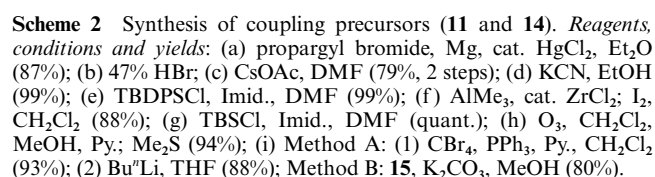
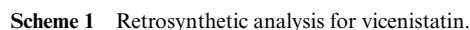
showed no cytotoxicity, which strongly suggested that the vicenisamine amino sugar plays an important role in exerting the antitumor activity of vicenistatin.

To explore the chemical features essential to its biological activities, we have been engaged in synthetic studies of vicenistatin. Previously, we reported the synthesis of the aglycone part.⁸ Furthermore, we have developed a new synthetic strategy for 2,6-dideoxyamino sugars, by which the synthesis of D-vicenisamine and L-kedariosamine was furnished.⁹ Along these lines, we report herein the enantioselective total synthesis of vicenistatin.

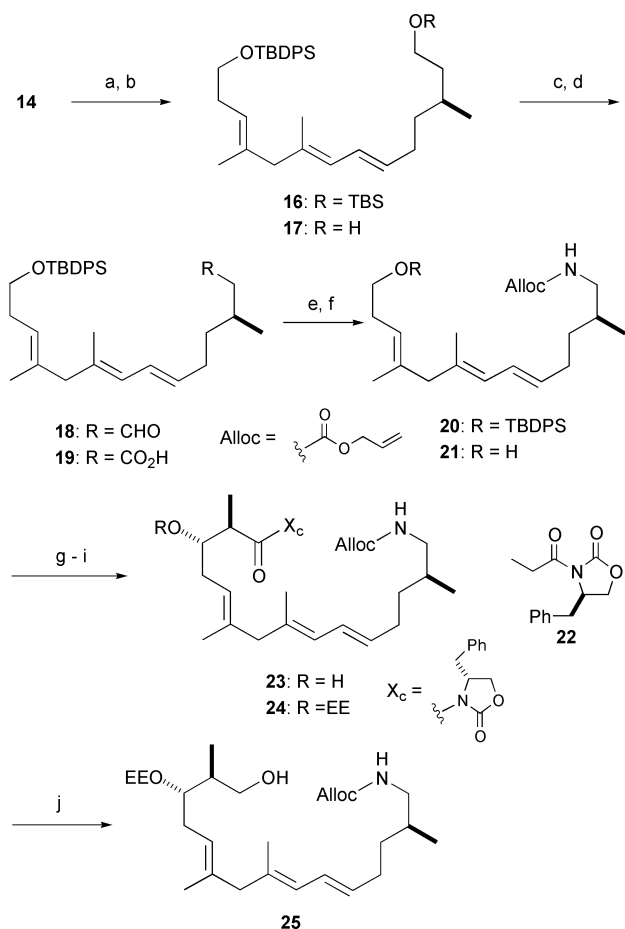
Our convergent synthetic plan, which should be flexible in view of possible future structure modifications, is shown in Scheme 1. The final stage of the synthesis was to be glycosidation, however, a difficulty had already been found in that the free aglycone was extremely insoluble in most solvents.⁷ Therefore, the aglycone part had to be prepared in a suitably protected form for glycosidation. Consequently, *O*-TMS (trimethylsilyl) protected aglycone **2** was envisaged as a glycosyl acceptor, and *N,O*-protected 1-*O*-acetyl sugar **3** was chosen as a glycosyl donor, because of the ease of preparation of the free 1-*O*-acetyl sugar and its usefulness in glycosidation with *O*-TMS-alcohol.^{7,10} Accordingly, our previous synthetic strategy through the *N*-PMB (*p*-methoxybenzyl)-protected aglycone⁸ was modified for the synthesis of *O*-TMS-aglycone **2**, especially about the time point of introduction of the nitrogen functional group. We further envisaged that lactam formation should be as the final macrocyclization for the aglycone. The crucial precursor **A** was expected to be synthesized from the triene-alcohol **B** by Evans asymmetric aldol reaction¹¹ and subsequent Wittig–Horner chain elongation, and the intermediate **B** seemed to be stereoselectively constructable by Suzuki cross-coupling¹² of **C** and **D**. The vinyl iodide **C** should be derived from cyclopropyl methyl ketone **4**, and the vinylboronate counterpart **D** could be derived from (*S*)-citronellol **5** via a corresponding acetylene **D'**.

Results and discussion

According to the above-mentioned strategy, our work started from the preparation of two components, **C** (\equiv **11**) and **D'** (\equiv **14**), which is depicted in Scheme 2. The homopropargyl alcohol **6**, which was obtained from cyclopropyl methyl ketone



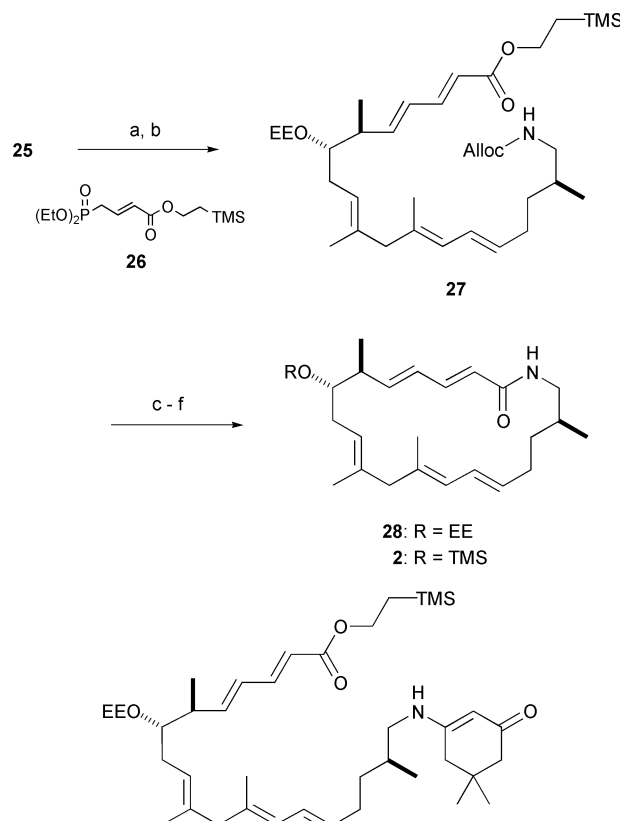
Subsequent key manipulations included construction of two contiguous chiral centers (C-6, -7) (Scheme 3), chain elongation



Scheme 3 Synthesis of *O*-TMS-aglycone (2)-1. *Reagents, conditions and yields:* (a) catecholborane, THF; **11**, cat. Pd(PPh₃)₄, 2 M NaOH, benzene (72% from **11**); (b) AcOH, H₂O, THF (60%); (c) (COCl)₂, DMSO; Et₃N, CH₂Cl₂ (82%); (d) NaClO₂, 2-methylbut-2-ene, NaH₂PO₄, Bu^tOH, H₂O (99%); (e) (PhO)₂P(O)N₃, Et₃N; allyl alcohol, benzene (68%); (f) HF·Py, THF (89%); (g) Dess–Martin periodinane, CH₂Cl₂; (h) **22**, Bu^tBOTf, Et₃N, CH₂Cl₂ (62%, 2 steps); (i) EVE, PPTS, CH₂Cl₂ (86%); (j) LiBH₄, MeOH, THF (74%).

(C-1–C-5) and the final macrolactamization (Scheme 4). Dess–Martin oxidation²³ of the alcohol **21** gave the corresponding aldehyde, but considerable decomposition was observed during the work-up and purification. Therefore, the highly unstable aldehyde had to be immediately subjected to Evans aldol reaction.¹¹ Thus, a reaction mixture of the oxidation was directly injected into a boron enolate solution, which previously had been prepared from chiral oxazolidinone **22**, to give an aldol product **23** in moderate yield. After protection of the resulting 7-hydroxy group as its 1-ethoxyethyl (EE) ether, compound **24** was reduced with lithium borohydride to give primary alcohol **25**. The alcohol **25** was then oxidized by Dess–Martin procedure to give the corresponding aldehyde, which in turn was subjected to Wittig–Horner chain elongation with phosphonate **26** to give (*E,E*)-diene ester **27**.

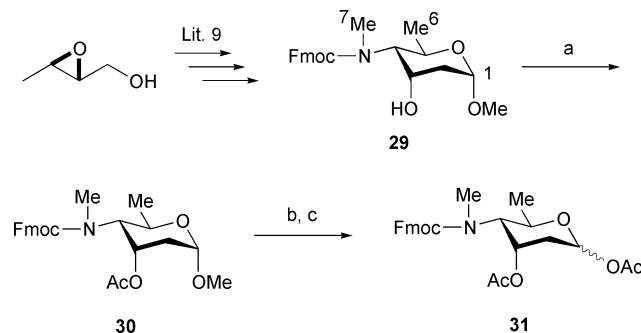
Removal of amino- and carboxy-protecting groups and subsequent macrolactamization were performed as follows. Initial palladium-catalyzed deprotection of the Alloc group of **27** was somewhat troublesome, *i.e.* the deprotected free amine happened to react with dimedone, which was the generally used allyl-transfer reagent, to form an enamine (*m/z* 669 [*M* – H][–]) as a by-product shown in Scheme 4.²⁴ Fortunately, this side reaction could be avoided by using 2-ethylhexanoic acid²⁵ or, more favorably, 1,3-dimethylbarbituric acid²⁶ as allyl-transfer reagent in the presence of tetrakis(triphenylphosphine)palladium to yield an intermediary seco-ester. The remaining TMS-ethyl protecting group of the seco-ester was immediately cleaved by tetra-*n*-butylammonium fluoride (TBAF) to give an



Scheme 4 Synthesis of *O*-TMS-aglycone (2)-2. *Reagents, conditions and yields:* (a) Dess–Martin periodinane, CH₂Cl₂; (b) **26**, LiN(TMS)₂, THF (58%, 2 steps); (c) Pd(PPh₃)₄, dimethylbarbituric acid, THF (65%); (d) TBAF, THF; (e) (EtO)₂P(O)CN, Et₃N, DMF (28%, 2 steps); (f) PPTS, MeOH; TMSCl, Et₃N, DMAP, CH₂Cl₂ (92%).

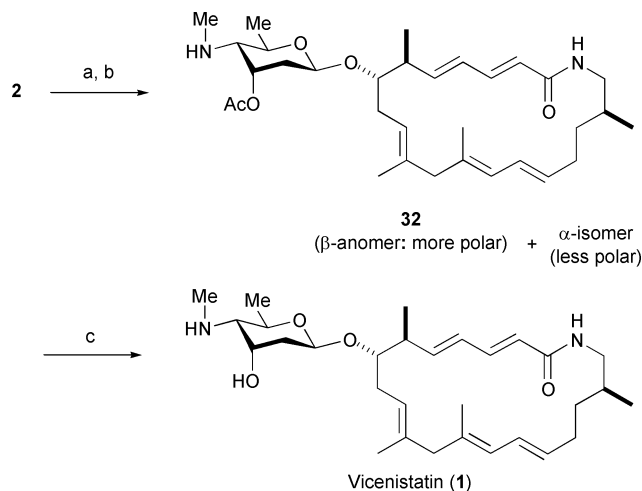
ω-amino carboxylic acid, the precursor for the macrolactamization. Subsequently, the final cyclization was successfully performed under high dilution (0.002 M) in DMF with diethyl cyanophosphonate and triethylamine at 0 °C (Shioiri's conditions for peptide synthesis²⁷) to construct the macrolactam ring **28** (28%, 2 steps). The EE protecting group of **28** was finally removed by acid-catalyzed methanolysis and the resulting 7-hydroxy group was immediately reprotected to give the desired *O*-TMS-aglycone **2**. Its spectroscopic properties were identical with those of an authentic specimen, which was obtained from natural vicenistatin (**1**) in two steps, *i.e.* acidic solvolysis and *O*-TMS protection.⁷ At this stage, we were successful in synthesizing the 20-membered macrocyclic lactam, *O*-TMS-aglycone (**2**) as the glycosyl acceptor.

The glycosyl donor was then prepared from *N*-Fmoc (fluoren-9-ylmethoxycarbonyl)-protected methyl α-vicenisaminide **29**, the synthesis of which was recently reported.⁹ Thus, the C-3 hydroxy group of **29** was first protected as an acetate **30** (Scheme 5). After hydrolysis of **30** in aqueous acetic acid, the



Scheme 5 Synthesis of glycosyl donor. *Reagents, conditions and yield:* (a) Ac₂O, DMAP, Py. (89%); (b) AcOH, H₂O; (c) Ac₂O, DMAP, Py. (97%, 2 steps).

resulting free sugar was further acetylated to give the desired glycosyl donor 1,3-di-*O*-acetyl-*N*-Fmoc-vicenisamine **31**. It turned out that these *N*-Fmoc-protected compounds bore a slight disadvantage in that slow rotation around the urethane C–N bond resulted in complicated NMR spectra due to the presence of rotational isomers. However, the Fmoc protecting group was chosen because of its ease of removal in the final stage of the synthesis (See Scheme 6).



Scheme 6 Synthesis of vicenistatin (**1**). *Reagents, conditions and yields:* (a) SnCl_4 , AgClO_4 , **31** CH_2Cl_2 , 0°C (59% from **2**); (b) DBU, EtOAc: PLC separation (**32**: 46%; α-isomer: 46%); (c) conc KOH aq., MeOH, rt (83%).

Glycosidation of the *O*-TMS-aglycone **2** with **31** was achieved using Mukaiyama's protocol.¹⁰ In the event, treatment of an ice-cooled solution of **2** and **31** in dry CH_2Cl_2 in the presence of SnCl_4 – AgClO_4 , followed by warming of the heterogeneous mixture, provided an inseparable anomeric mixture in 59% yield as shown in Scheme 6. The Fmoc protective group of the mixture was subsequently cleaved with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)²⁸ to afford the desired β-glycoside **32** (1'-H: dd, $J = 1.8, 9.8$ Hz) and an α-anomer (1'-H: d, $J = 4.2$ Hz), which were separated by preparative thin-layer chromatography (PLC) (α : β ≈ 1 : 1). The 3'-*O*-acetyl group of the thus obtained β-glycoside **32** was deprotected by alkaline hydrolysis to afford vicenistatin (**1**). All the spectral data of the synthetic **1** were identical in every aspect to those of natural vicenistatin.

In conclusion, we were successful in enantioselectively synthesizing vicenistatin. The convergent synthetic strategy described above appears to be applicable to the synthesis of various vicenistatin derivatives.

Experimental

All mps are uncorrected. NMR spectra were recorded on a JEOL LA-300, or a Bruker DRX-500 spectrometer. ^1H -NMR and ^{13}C -NMR chemical shifts were reported in δ -values based on internal tetramethylsilane ($\delta_{\text{H}} = 0$), or solvent signal (CDCl_3 , $\delta_{\text{C}} = 77.0$; pyridine- d_5 , $\delta_{\text{H}} = 7.20$, $\delta_{\text{C}} = 135.5$) as reference. IR spectra were recorded on a Horiba FT-710 Fourier-transform infrared spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter, and $[\alpha]_{\text{D}}$ -values are given in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Mass spectra were measured on a JEOL AX-505HA mass spectrometer. Silica gel column chromatography was carried out with Merck Kieselgel 60, Art. Nr. 7734, and flash column chromatography was carried out with Merck Kieselgel 60, Art. Nr. 9385.

2-Cyclopropylpent-4-yn-2-ol **6**

To a suspension of magnesium turnings (2.66 g, 110 mmol) and mercury(II) chloride (24.2 mg, 8.91×10^{-2} mmol, 0.15

mol%) in dry Et_2O (80 cm^3) was added dropwise propargyl bromide (6.92 cm^3 , 91.9 mmol) at a rate to maintain gentle reflux under Ar. To an ice-cooled solution of the resulting Grignard reagent was added dropwise a solution of cyclopropyl methyl ketone **4** (5.00 g, 59.4 mmol) in dry Et_2O (15 cm^3) and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by addition of saturated aq. NH_4Cl at 0°C , and the resulting mixture was extracted four times with Et_2O . The combined extract was washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was vacuum-distilled at 80.5 – 81.0°C (32 mmHg) to give compound **6** as a colorless oil (6.42 g, 87%) {HREIMS m/z 124.0842 [(M)⁺; Calc. for $\text{C}_8\text{H}_{12}\text{O}$: m/z , 124.0888]}; ν_{max} (neat)/ cm^{-1} 3423 (br), 3303, 3086, 2117, 1375 and 636; δ_{H} (300 MHz; CDCl_3) 0.33–0.48 (m, 4H), 0.99–1.09 (m, 1H), 1.24 (s, 3H), 2.09 (t, $J = 2.2$ Hz, 1H) and 2.38–2.51 (m, 2H); δ_{C} (75 MHz; CDCl_3) 0.03, 0.23, 19.9, 25.0, 32.7, 69.5, 70.5 and 80.4.

(*E*)-7-Acetoxy-4-methylhept-4-en-1-yne **8**

To a solution of 47% aq. HBr (15 cm^3) was added dropwise the alcohol **6** (6.40 g, 51.5 mmol) at -24°C . After the reaction mixture had been stirred for 3 hr at 0°C , it was extracted four times with pentane. The combined extract was washed successively with saturated aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated *in vacuo*. The residual crude bromide **7** (9.26 g, 96%) was immediately used for the next step without further purification.

To a solution of bromide **7** (9.26 g, ≈ 49.5 mmol) in dry DMF (20 cm^3) was added caesium acetate (15.0 g, 78.1 mmol) and the reaction mixture was stirred for 19 h at rt. The mixture was poured into water and extracted four times with Et_2O . The combined extract was washed successively with water, saturated aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 50 : 1 to 20 : 1) to give acetate **8** as a colorless oil (6.77 g, 79% in 2 steps) {HREIMS m/z 166.0966 [(M)⁺; Calc. for $\text{C}_{10}\text{H}_{14}\text{O}_2$: m/z , 166.0994]}; ν_{max} (neat)/ cm^{-1} 3284, 2117, 1739, 1245 and 1036; δ_{H} (300 MHz; CDCl_3) 1.72 (s, 3H), 2.05 (s, 3H), 2.09 (t, $J = 2.2$ Hz, 1H), 2.38 (q, $J = 6.6$ Hz, 2H), 2.91 (s, 2H), 4.07 (dt, $J = 7.1, 2.5$ Hz, 2H) and 5.43 (dt, $J = 7.1, 1.2$ Hz, 1H); δ_{C} (75 MHz; CDCl_3) 16.0, 20.9, 27.5, 28.5, 63.7, 70.4, 81.6, 120.9, 132.6 and 171.1.

(*E*)-4-Methylhept-3-en-6-yn-1-ol **9**

A solution of acetate **8** (4.14 g, 24.5 mmol) and potassium cyanide (1.36 g, 20.0 mmol) in ethanol (83 cm^3) was stirred for 5 days at rt. The reaction was quenched by addition of water (30 cm^3), and the solvent was removed *in vacuo*. The residue was dissolved in water and extracted three times with Et_2O . The combined extract was washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 10 : 1 to 5 : 1) to give alcohol **9** as a colorless oil (3.07 g, 99%) {HREIMS m/z 124.0930 [(M)⁺; Calc. for $\text{C}_8\text{H}_{12}\text{O}$: m/z , 124.0888]}; ν_{max} (neat)/ cm^{-1} 3373 (br), 3298, 2117, 1421 and 1047; δ_{H} (300 MHz; CDCl_3) 1.73 (s, 3H), 2.13 (t, $J = 2.4$ Hz, 1H), 2.38 (q, $J = 6.4$ Hz, 2H), 2.92 (s, 2H), 3.65 (dt, $J = 7.1, 2.5$ Hz, 2H) and 5.46 (dt, $J = 7.1, 1.2$ Hz, 1H); δ_{C} (75 MHz; CDCl_3) 16.2, 28.5, 31.5, 62.2, 70.5, 81.7, 121.8 and 132.7.

(*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4-methylhept-4-en-1-yne **10**

To an ice-cooled solution of alcohol **9** (523.3 mg, 4.21 mmol) and imidazole (456 mg, 6.70 mmol) in DMF (5 cm^3) was added dropwise *tert*-butyldiphenylsilyl chloride (1.26 cm^3 , 4.85 mmol) and the mixture was stirred for 0.5 h at 0°C . The reaction mixture was poured into cold water and the mixture was extracted twice with pentane. The combined extract was washed successively with saturated aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was

purified by column chromatography (hexane–Et₂O, 50 : 1) to give silyl ether **10** as a colorless oil (1.51 g, 99%) (Found: C, 79.37; H, 8.42. Calc. for C₂₄H₃₀OSi: C, 79.50; H, 8.34%); ν_{\max} (neat)/cm⁻¹ 3309, 2119, 1427, 1113, 823 and 702; δ_{H} (300 MHz; CDCl₃) 1.05 (s, 9H), 1.63 (s, 3H), 2.07 (t, $J = 2.7$ Hz, 1H), 2.30 (q, $J = 6.8$ Hz, 2H), 2.86 (s, 2H), 3.66 (t, $J = 6.8$ Hz, 2H), 5.46 (tt, $J = 1.4, 7.3$ Hz, 1H), 7.28–7.43 (m, 6H) and 7.66–7.69 (m, 4H); δ_{C} (75 MHz; CDCl₃) 16.0, 19.1, 26.8, 28.5, 31.5, 63.4, 70.3, 81.9, 122.4, 127.6, 129.5, 131.3, 134.0 and 135.6.

(1E,4E)-7-(tert-Butyldiphenylsilyloxy)-2,4-dimethyl-1-iodohepta-1,4-diene 11

To an ice-cooled suspension of dichlorobis(η^5 -pentadienyl)-zirconium (156 mg, 5.34×10^{-1} mmol) in dry CH₂Cl₂ (2.5 cm³) were added dropwise a solution of alkyne **10** (865 mg, 2.39 mmol) in dry CH₂Cl₂ (3.0 cm³) and trimethylaluminum (2.50 cm³, 2.0 M solution in toluene, 5.0 mmol) in that order under Ar. The resulting mixture was warmed to rt and stirred for an additional 5.5 h. To the mixture was added dropwise a solution of iodine (940 mg, 3.70 mmol) in THF (3 cm³) at 0 °C and the mixture was stirred at the same temperature for 1 h. The reaction was carefully quenched by addition of cold water and the mixture was extracted twice with pentane. The combined extract was washed successively with 0.5 M HCl, saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 100 : 1) to give iodide **11** as a colorless oil (1.06 g, 88%) {HREIMS m/z 505.1389 [(M)⁺]; Calc. for C₂₅H₃₄IOSi: m/z , 505.1424}; ν_{\max} (neat)/cm⁻¹ 3070, 1589, 1471, 1427, 1110 and 701; δ_{H} (300 MHz; CDCl₃) 1.04 (s, 9H), 1.47 (s, 3H), 1.73 (s, 3H), 2.28 (q, $J = 7.3$ Hz, 2H), 2.82 (s, 2H), 3.65 (t, $J = 6.8$ Hz, 2H), 5.21 (t, $J = 7.3$ Hz, 1H), 5.90 (s, 1H), 7.24–7.45 (m, 6H) and 7.65–7.69 (m, 4H); δ_{C} (75 MHz; CDCl₃) 15.5, 19.2, 23.3, 26.8, 31.6, 49.8, 63.5, 75.8, 123.8, 127.6, 129.5, 133.5, 134.0, 135.6 and 146.2.

(S)-8-tert-Butyldimethylsilyloxy-2,6-dimethyloct-2-ene [(S)-citronellol tert-butyldimethylsilyl ether] 12

To an ice-cooled solution of (S)-citronellol **5** (147.0 g, 941 mmol) and imidazole (96.1 g, 1.41 mol) in dry DMF (750 cm³) was added portionwise *tert*-butyldimethylsilyl chloride (165.7 g, 1.10 mol). The mixture was stirred for 3 h at 0 °C. The reaction mixture was poured into water and the mixture was extracted three times with Et₂O. The combined extract was washed with brine, dried over (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 50 : 1) to give silyl ether **12** as a colorless oil (266.9 g, quant.) (Found: C, 71.21; H, 12.72; Calc. for C₁₆H₃₄OSi: C, 71.04; H, 12.67%); $[\alpha]_{\text{D}}^{24} -1.42$ (c 1.01, CHCl₃); ν_{\max} (neat)/cm⁻¹ 2956, 2857, 1471, 1255 and 1097; δ_{H} (300 MHz; CDCl₃) 0.05 (s, 6H), 0.89 (d, $J = 10$ Hz, 3H), 0.90 (s, 9H), 1.08–1.20 (m, 1H), 1.29–1.39 (m, 2H), 1.50–1.56 (m, 2H), 1.58 (s, 3H), 1.68 (s, 3H), 1.90–2.05 (m, 2H), 3.57–3.70 (m, 2H) and 5.10 (t, $J = 7.3$ Hz, 1H); δ_{C} (75 MHz; CDCl₃) –5.3, 17.5, 18.3, 19.6, 25.5, 25.7, 26.0, 29.1, 37.3, 40.0, 61.3, 125.0 and 130.7.

(S)-6-tert-Butyldimethylsilyloxy-4-methylhexanal 13

To a mixture of alkene **12** (35.2 g, 129 mmol), MeOH (120 cm³), CH₂Cl₂ (120 cm³), and pyridine (2 cm³) was introduced ozone at –78 °C until the color of the resulting solution became pale blue. Excess ozone was purged with a stream of argon, and dimethyl sulfide (11.0 cm³, 150 mmol) was added dropwise to the mixture at –78 °C. The solution was allowed to warm gradually to rt with stirring for 18 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (hexane–EtOAc, 20 : 1) to give aldehyde **13** as a colorless oil (29.9 g, 94%) (Found: C, 63.66; H, 11.64. Calc. for C₁₃H₂₈O₂Si: C, 63.88; H, 11.54%); $[\alpha]_{\text{D}}^{20} +5.38$ (c 1.86,

CHCl₃); ν_{\max} (neat)/cm⁻¹ 2713, 1728, 1471, 1463, 1255 and 1095; δ_{H} (300 MHz; CDCl₃) 0.05 (s, 6H), 0.89 (d, $J = 10$ Hz, 3H), 0.84 (s, 9H), 1.34–1.74 (m, 5H), 2.40–2.47 (m, 2H), 3.58–3.70 (m, 2H) and 9.78 (t, $J = 1.7$ Hz, 1H); δ_{C} (75 MHz; CDCl₃) –5.3, 17.5, 18.3, 19.6, 25.5, 25.7, 26.0, 29.1, 37.3, 40.0, 61.3, 125.0 and 130.7.

(S)-7-tert-Butyldimethylsilyloxy-5-methylhept-1-yne 14

Method A. To an ice-cooled solution of triphenylphosphine (86.1 g, 328 mmol) in CH₂Cl₂ (600 cm³) and pyridine (16 cm³) was added portionwise carbon tetrabromide (52.6 g, 159 mmol). After the mixture had been stirred for 10 min, a solution of aldehyde **13** (20.0 g, 81.8 mmol) in CH₂Cl₂ (20 cm³) was added over a period of 10 min. The mixture was stirred for 2 h at 0 °C, and was then poured into a stirred mixture of hexane and saturated aq. NaHCO₃. The whole was extracted three times with hexane. The combined extract was washed twice with brine, dried (MgSO₄) and concentrated *in vacuo*. Insoluble material was filtered off when generated during the concentration. The residue was purified by column chromatography (hexane–EtOAc, 30 : 1) to give an intermediary dibromo olefin as a colorless oil (30.6 g, 93%) (Found: C, 42.24; H, 7.22. Calc. for C₁₄H₂₈Br₂OSi: C, 42.01; H, 7.05%); $[\alpha]_{\text{D}}^{25} -1.51$ (c 1.27, CHCl₃); ν_{\max} (neat)/cm⁻¹ 2954, 2856, 1625, 1471, 1461, 1255 and 1095; δ_{H} (300 MHz; CDCl₃) 0.05 (s, 6H), 0.89 (s, 9H), 0.90 (d, $J = 6.1$ Hz, 3H), 1.20–1.65 (m, 5H), 2.02–2.18 (m, 2H), 3.60–3.69 (m, 2H) and 6.37 (t, $J = 7.3$ Hz, 1H); δ_{C} (75 MHz; CDCl₃) –5.3, 18.3, 19.4, 26.0, 29.0, 30.6, 34.9, 40.0, 61.1, 88.5 and 138.8.

To a solution of the dibromo olefin (21.47 g, 53.7 mmol) in THF (250 cm³) was added dropwise *n*-butyllithium (87.5 cm³; 1.53 M solution in hexane, 134 mmol) at –78 °C. The solution was then stirred for 1 h at –78 °C, and for 3.5 h at rt. Saturated aq. NH₄Cl (30 cm³) was added slowly to the mixture. The solvent was removed *in vacuo*. The residue was diluted with Et₂O (40 cm³) and water (50 cm³). The aqueous layer was extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 50 : 1) to give alkyne **14** as a colorless oil (11.34 g, 88%) (Found: C, 69.67; H, 11.52. Calc. for C₁₄H₂₈OSi: C, 69.93; H, 11.74%); $[\alpha]_{\text{D}}^{26} -0.07$ (c 1.19, CHCl₃); ν_{\max} (neat)/cm⁻¹ 3315, 2119, 1255 and 1093; δ_{H} (300 MHz; CDCl₃) 0.01 (s, 6H), 0.84 (s, 9H), 0.85 (d, $J = 4.4$ Hz, 3H), 1.22–1.39 (m, 2H), 1.47–1.58 (m, 2H), 1.60–1.73 (m, 1H), 1.88 (t, $J = 2.5$ Hz, 1H), 2.12–2.21 (m, 2H) and 3.55–3.67 (m, 2H); δ_{C} (75 MHz; CDCl₃) –5.3, 16.1, 18.3, 19.1, 25.9, 28.8, 35.7, 39.5, 61.2, 68.0 and 84.7.

Method B. To a solution of aldehyde **13** (1.59 g, 6.50 mmol) and potassium carbonate (1.81 g, 13.1 mmol) in MeOH (98 cm³) was added dimethyl (1-diazo-2-oxopropyl)phosphonate **15**¹⁸ (1.52 g, 7.91 mmol). The reaction mixture was stirred for 5 h at rt. After the solvent had been removed *in vacuo*, the residue was suspended in water and extracted twice with Et₂O. The combined extract was washed successively with saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane) to afford alkyne **14** (1.26 g, 80%).

(3E,6E,8E,12S)-14-tert-Butyldimethylsilyloxy-1-tert-butyl-diphenylsilyloxy-4,6,12-trimethyltetradeca-3,6,8-triene 16

To a solution of alkyne **14** (10.52 g, 43.78 mmol) in THF (120 cm³) was added catecholborane (52.2 cm³; 1.0 M solution in THF, 52 mmol) and the mixture was refluxed for 3 h. After the solvent had been removed *in vacuo*, the residue was dissolved in benzene (100 cm³). To the solution were added the vinyl iodide **11** (20.08 g, 39.80 mmol), tetrakis(triphenylphosphine)palladium (1.45 g, 1.25 mmol, 3 mol%), and 2 M NaOH (43 cm³) and the resulting mixture was refluxed for 10 h.

After the solution had been cooled to 0 °C, a mixture of 35% H₂O₂ (15 cm³) and 2 M NaOH (22 cm³) was added slowly. The solvent was then removed *in vacuo* and the residue was extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 100 : 1) to give triene **16** as a colorless oil (17.86 g, 72% from **11**), which was used for the next reaction without further purification; ν_{max} (neat)/cm^{−1} 1471, 1255, 1110 and 701; δ_{H} (300 MHz; CDCl₃) 0.06 (s, 6H), 0.87–0.90 (m, 12H), 1.02 (s, 9H), 1.21–1.76 (m, 11H), 2.05–2.15 (m, 2H), 2.25–2.32 (m, 2H), 2.66 (s, 2H), 3.60–3.71 (m, 4H), 5.18 (dt, $J = 7.1, 1.2$ Hz, 1H), 5.57 (dt, $J = 7.1, 15.1$ Hz, 1H), 5.79 (d, $J = 10.7$ Hz, 1H), 6.23 (dd, $J = 10.7, 15.1$ Hz, 1H), 7.34–7.45 (m, 6H, aromatic) and 7.66–7.70 (m, 4H, aromatic); δ_{C} (75 MHz; CDCl₃) −5.2, 15.6, 15.9, 19.2, 19.6, 26.0, 26.8, 29.1, 30.4, 31.7, 36.9, 39.8, 50.4, 61.4, 63.7, 122.5, 126.2, 126.5, 127.6, 129.5, 132.8, 134.0, 134.4, 134.9 and 135.6.

(3S,6E,8E,11E)-14-tert-Butyldiphenylsilyloxy-3,9,11-trimethyl-tetradeca-6,8,11-trien-1-ol 17

A mixture of bis-silyl ether **16** (1.48 g, 2.38 mmol) in THF (9 cm³), acetic acid (20 cm³) and water (4 cm³) was stirred for 40 h at rt. To the solution was added dropwise conc. aq. NaOH (13.9 g in 40 cm³ of water) at 0 °C. The whole mixture was extracted four times with Et₂O. The combined extract was washed successively with saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 20 : 1 to 5 : 1) to give alcohol **17** as a colorless oil (722 mg, 60%) (Found: C, 78.31; H, 9.88. Calc. for C₃₃H₄₈O₂Si: C, 78.51; H, 9.58%; $[\alpha]_{\text{D}}^{25} -1.18$ (c 1.50, CHCl₃); ν_{max} (neat)/cm^{−1} 1471, 1255, 1110 and 701; δ_{H} (300 MHz; CDCl₃) 0.87 (d, $J = 6.8$ Hz, 3H), 1.04 (s, 9H), 1.17–1.66 (m, 11H), 2.05–2.15 (m, 2H), 2.29 (q, $J = 7.1$ Hz, 2H), 2.65 (s, 2H), 3.65 (t + overlapping signals, $J = 7.0$ Hz, 4H), 5.18 (dt, $J = 7.3, 1.1$ Hz, 1H), 5.55 (dt, $J = 15.1, 7.3$ Hz, 1H), 5.79 (d, $J = 10.7$ Hz, 1H), 6.23 (ddt, $J = 10.7, 15.1, 1.5$ Hz, 1H), 7.34–7.44 (m, 6H, aromatic) and 7.66–7.70 (m, 4H, aromatic); δ_{C} (75 MHz; CDCl₃) 15.6, 15.9, 19.1, 19.4, 26.8, 29.0, 30.3, 31.6, 36.8, 39.8, 50.3, 61.0, 63.7, 122.5, 126.2, 126.6, 127.5, 129.5, 132.6, 134.0, 134.5, 135.0 and 135.5.

(3S,6E,8E,11E)-14-tert-Butyldiphenylsilyloxy-3,9,11-trimethyl-tetradeca-6,8,11-trien-al 18

A solution of Swern reagent was prepared by dropwise addition of DMSO (2.00 cm³, 28.2 mmol) to a stirred solution of oxalyl dichloride (7.34 cm³, 2.0 M solution in CH₂Cl₂, 14.7 mmol) in CH₂Cl₂ (60 cm³) at −78 °C under Ar and stirring was continued for 30 min. To the solution was added dropwise a solution of alcohol **17** (4.95 g, 9.78 mmol) in CH₂Cl₂ (20 cm³) at −78 °C, and the mixture was stirred for 30 min. Triethylamine (5.40 cm³, 38.7 mmol) was added to the mixture at −78 °C, and the temperature was allowed to rise gradually to rt over 2 h. The mixture was poured into water and extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 10 : 1) to give aldehyde **18** as a colorless oil (3.63 g, 82%) (Found: C, 78.71; H, 9.40. Calc. for C₃₃H₄₆O₂Si: C, 78.83; H, 9.22%; $[\alpha]_{\text{D}}^{25} -11.5$ (c 1.60, CHCl₃); ν_{max} (neat)/cm^{−1} 2713, 1726, 1427 and 1110; δ_{H} (300 MHz; CDCl₃) 0.97 (d, $J = 6.6$ Hz, 3H), 1.04 (s, 9H), 1.27–1.69 (m, 9H), 2.11 (q, $J = 6.8$ Hz, 2H), 2.20–2.32 (m, 2H), 2.41 (ddd, $J = 2.0, 3.8, 11.9$ Hz, 2H), 2.66 (s, 2H), 3.65 (t, $J = 6.9$ Hz, 2H), 5.18 (d, $J = 6.7$ Hz, 1H), 5.54 (dt, $J = 15.0, 6.8$ Hz, 1H), 5.79 (d, $J = 10.5$ Hz, 1H), 6.24 (dd, $J = 10.5, 15.0$ Hz, 1H), 7.34–7.44 (m, 6H, aromatic), 7.66–7.70 (m, 4H, aromatic) and 9.75 (t, $J = 2.3$ Hz, 1H); δ_{C} (75 MHz; CDCl₃) 15.7, 16.0, 19.2, 26.8, 27.7, 30.3, 31.7, 36.6, 50.4, 51.0, 63.7, 122.6, 126.0, 127.1, 127.6, 129.5, 131.7, 134.0, 134.9, 135.6 and 202.9.

(3S,6E,8E,11E)-14-tert-Butyldiphenylsilyloxy-3,9,11-trimethyltetradeca-6,8,11-trienoic acid 19

To an ice-cooled solution of **18** (3.63 g, 7.22 mmol) in 2-methylbut-2-ene (40.0 cm³, 376 mmol) and *tert*-butyl alcohol (55 cm³) was added dropwise a solution of sodium chlorite (6.01 g, 665 mmol) and sodium dihydrogen phosphate dihydrate (7.83 g, 50.2 mmol) in water (65 cm³). The mixture was stirred for 30 min and extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 2 : 1 to 1 : 1) to give acid **19** (3.74 g, 99%) as a colorless oil (Found: C, 76.15; H, 9.05. Calc. for C₃₃H₄₆O₃Si: C, 76.40; H, 8.94%; $[\alpha]_{\text{D}}^{25} -5.23$ (c 1.03, CHCl₃); ν_{max} (neat)/cm^{−1} 3089, 2857, 1709, 1427, 1110 and 823; δ_{H} (300 MHz; CDCl₃) 0.98 (d, $J = 6.4$ Hz, 3H), 1.05 (s, 9H), 1.26–1.34 (m, 1H), 1.47 (s, 3H), 1.62 (s, 3H), 1.96–2.40 (m, 8H), 2.65 (s, 2H), 3.65 (t, $J = 6.9$ Hz, 2H), 5.18 (t, $J = 6.8$ Hz, 1H), 5.55 (dt, $J = 15.1, 6.9$ Hz, 1H), 5.79 (d, $J = 10.7$ Hz, 1H), 6.24 (dd, $J = 10.1, 15.1$ Hz, 1H), 7.23–7.39 (m, 6H) and 7.66–7.69 (m, 4H); δ_{C} (75 MHz; CDCl₃) 15.7, 16.0, 19.2, 19.5, 26.8, 29.7, 30.3, 31.7, 36.4, 41.5, 50.4, 63.7, 122.6, 126.1, 127.0, 127.6, 129.5, 131.9, 134.0, 134.8, 135.0, 135.6 and 179.6.

(3E,6E,8E,12S)-13-Allyloxycarbonylamino-1-tert-butyl-diphenylsilyloxy-4,6,12-trimethyltrideca-3,6,8-triene 20

A solution of acid **19** (3.73 g, 7.20 mmol), diphenylphosphoryl azide (1.87 cm³, 10.1 mmol), and triethylamine (1.20 cm³, 9.36 mmol) in benzene (60 cm³) was refluxed for 3 h. After addition of allyl alcohol (2.55 cm³, 39.6 mmol), the reaction mixture was refluxed again for another 24 h. The reaction was quenched by addition of water and the resulting mixture was extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 30 : 1) to give carbamate **20** (2.81 g, 68%) as a colorless oil (Found: C, 75.20; H, 8.99; N, 2.53. Calc. for C₃₆H₅₁NO₃: C, 75.34; H, 8.96; N, 2.44%; $[\alpha]_{\text{D}}^{28} -1.63$ (c 0.877, CHCl₃); ν_{max} (neat)/cm^{−1} 3070, 2856, 1703, 1427, 1113 and 739; δ_{H} (75 MHz; CDCl₃) 0.90 (d, $J = 6.4$ Hz, 3H), 1.05 (s, 9H), 1.26–1.34 (m, 2H), 1.47 (s, 3H), 1.62 (s, 3H), 1.96–2.40 (m, 8H), 3.65 (t, $J = 6.9$ Hz, 2H), 4.55 (d, $J = 5.6$ Hz, 2H), 4.73 (br s, 1H), 5.18 (d, $J = 6.8$ Hz, 1H), 5.21 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.30 (dq, $J = 17.3, 1.4$ Hz, 1H), 5.55 (dt, $J = 15.1, 6.9$ Hz, 1H), 5.79 (d, $J = 10.1$ Hz, 1H), 5.92 (ddt, $J = 10.4, 17.3, 5.6$ Hz, 1H), 6.23 (dd, $J = 10.1, 15.1$ Hz, 1H), 7.35–7.42 (m, 6H, aromatic) and 7.66–7.69 (m, 4H, aromatic); δ_{C} (75 MHz; CDCl₃) 15.6, 15.9, 17.3, 19.1, 26.8, 30.2, 31.6, 33.0, 33.9, 46.8, 50.3, 63.7, 65.4, 117.6, 122.5, 126.1, 126.9, 127.5, 129.5, 132.0, 133.0, 134.0, 134.8, 134.9, 135.5 and 156.4.

(3E,6E,8E,12S)-13-Allyloxycarbonylamino-4,6,12-trimethyl-trideca-3,6,8-trien-1-ol 21

To a solution of silyl ether **20** (808 mg, 1.41 mol) in THF (15 cm³) was added dropwise HF–pyridine (1.5 cm³; $\approx 70\%$ HF, 58 mmol) and the mixture was stirred for 6 h at rt before being carefully poured into saturated aq. NaHCO₃ and extracted twice with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc, 5 : 1 to 2 : 1) to give alcohol **21** as a colorless oil (422 mg, 89%) (Found: C, 71.35; H, 10.08; N, 3.93. Calc. for C₂₆H₃₃NO₃: C, 71.60; H, 9.91; N, 4.18%; $[\alpha]_{\text{D}}^{29} -2.19$ (c 0.42, CHCl₃); ν_{max} (neat)/cm^{−1} 3344 (br), 3018, 2875, 1701, 1537, 1250 and 1047; δ_{H} (300 MHz; CDCl₃) 0.91 (d, $J = 6.6$ Hz, 3H), 1.15–1.51 (m, 3H), 1.57–1.68 (m, 9H), 2.02–2.19 (m, 2H), 2.32 (q, $J = 6.8, 2$ Hz), 2.45 (s, 2H), 3.01 (quintet, $J = 7.1$ Hz, 1H), 3.63 (t, $J = 6.3$ Hz, 2H), 5.19 (d, $J = 6.8$ Hz, 1H), 5.21 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.30 (dq, $J = 17.3, 1.4$ Hz, 1H), 5.57 (dt, $J = 15.1, 6.9$ Hz, 1H), 5.81 (d, $J =$

10.7 Hz, 1H), 5.93 (ddt, $J = 10.4, 17.3, 5.6$ Hz, 1H) and 6.24 (dd, $J = 10.7, 15.1$ Hz, 1H); δ_{C} (75 MHz; CDCl_3) 15.7, 15.9, 17.3, 30.1, 31.6, 33.0, 33.8, 46.8, 50.3, 62.3, 65.4, 117.5, 121.9, 126.2, 126.8, 132.2, 132.9, 134.3, 136.5 and 156.4.

(4R)-3-[(2R,3S,5E,8E,10E,14S)-15-Allyloxycarbonylamino-3-hydroxy-1,2,6,8,14-tetramethylpentadeca-5,8,10-trienoyl]-4-benzylloxazolidin-2-one 23

To a solution of alcohol **21** (1.58 g, 4.71 mmol) in CH_2Cl_2 (42 cm^3) was added Dess–Martin periodinane (2.82 g, 6.65 mmol). The mixture was stirred for 45 min at rt. The resulting aldehyde solution was kept at 0 °C until it was used for the next step.

To a solution of chiral oxazolidinone **22**¹¹ (1.57 g, 6.73 mmol) in CH_2Cl_2 (28 cm^3) were successively added dropwise di(*n*-butyl)boryl trifluoromethanesulfonate (7.65 cm^3 ; 1.0 M solution in CH_2Cl_2 , 7.7 mmol) and triethylamine (1.19 cm^3 , 8.54 mmol) at below –8 °C. To the resulting solution was added dropwise the above aldehyde solution at below –70 °C. The mixture was stirred for 50 min at –78 °C and then for 2 h at 0 °C. The reaction was quenched by addition of phosphate buffer (pH 7.4; 18.4 cm^3) and methanol (6.1 cm^3). To the mixture was added a 2 : 1 mixture of methanol–35% H_2O_2 (18.2 cm^3) at such a rate as to keep the internal temperature below 8 °C. After stirring for an additional 1 h, the mixture was evaporated *in vacuo*. The resulting slurry was extracted three times with Et_2O . The combined extract was washed successively with saturated aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane– EtOAc , 2 : 1) to give alcohol **23** as a colorless oil (1.65 g, 62% from **21**) (Found: C, 69.64; H, 8.31; N, 4.97. Calc. for $\text{C}_{33}\text{H}_{46}\text{N}_2\text{O}_6$: C, 69.94; H, 8.18; N, 4.94%; $[\alpha]_{\text{D}}^{25} -42.7$ (c 0.375, CHCl_3); ν_{max} (neat)/ cm^{-1} 3388 (br), 1782, 1722, 1242 and 704; δ_{H} (300 MHz; CDCl_3) 0.91 (d, $J = 6.5$ Hz, 3H), 1.28 (d, $J = 6.8$ Hz, 3H), 1.42–1.64 (m, 6H), 2.05–2.40 (m, 7H), 2.70 (s, 2H), 2.79 (dd, $J = 9.5, 13.2$ Hz, 1H), 2.97–3.15 (m, 2H), 3.25 (dd, $J = 3.2, 13.2$ Hz, 1H), 3.89 (dt, $J = 3.2, 6.9$ Hz, 1H), 4.00 (br s, 1H), 4.18–4.23 (m, 2H), 4.56 (br d, $J = 5.6$ Hz, 2H), 4.64–4.71 (m, 1H), 4.85 (br s, 1H), 5.18 (d, $J = 6.8$ Hz, 1H), 5.20 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.29 (dq, $J = 17.3, 1.4$ Hz, 1H), 5.56 (dt, $J = 15.1, 6.8$ Hz, 1H), 5.80 (d, $J = 10.7$ Hz, 1H), 5.92 (ddt, $J = 10.7, 17.3, 5.6$ Hz, 1H), 6.23 (dd, $J = 10.7, 15.1$ Hz, 1H) and 7.20–7.34 (m, 5H, aromatic); δ_{C} (75 MHz; CDCl_3) 10.6, 15.8, 16.0, 17.3, 30.1, 32.6, 33.0, 33.9, 37.7, 41.5, 46.9, 50.4, 55.1, 65.4, 66.1, 71.5, 117.6, 121.6, 126.3, 126.9, 127.4, 129.0, 129.4, 132.2, 133.0, 134.5, 135.0, 136.5, 152.9, 156.4 and 177.3.

(4R)-3-[(2R,3S,5E,8E,10E,14S)-15-Allyloxycarbonylamino-3-(1-ethoxyethoxy)-2,6,8,14-tetramethylpentadeca-5,8,10-trienoyl]-4-benzylloxazolidin-2-one 24

To a solution of alcohol **23** (1.65 g, 2.91 mmol) in ethyl vinyl ether (EVE) (45 cm^3) and CH_2Cl_2 (25 cm^3) was added pyridinium toluene-*p*-sulfonate (PPTS, 160 mg, 6.37×10^{-1} mmol) at 0 °C. After being warmed to rt, the solution was stirred for 1.5 h. The reaction was quenched by addition of saturated aq. NaHCO_3 and the aqueous layer was extracted twice with Et_2O . The combined extract was washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The reaction mixture was purified by flash chromatography (hexane– EtOAc , 10 : 1) to give the ether **24** as a colorless oil (1.77 g, 86%) (Found: C, 69.51; H, 8.70; N, 4.17. Calc. for $\text{C}_{37}\text{H}_{54}\text{N}_2\text{O}_7$: C, 69.56; H, 8.52; N, 4.39%; $[\alpha]_{\text{D}}^{25} -42.7$ (c 0.375, CHCl_3); ν_{max} (neat)/ cm^{-1} 3388 (br), 1782, 1722, 1242 and 704; δ_{H} (300 MHz; CDCl_3) 0.91 (d, $J = 6.8$ Hz, 3H), 1.15–1.30 (m, 12H), 1.63 (s, 3H), 1.67 (s, 2H), 2.05–2.25 (m, 2H), 2.30–2.37 (m, 2H), 2.68 (s, 2H), 2.76 (ddd, $J = 2.2, 9.9, 13.0$ Hz, 1H), 2.90 (m, 2H), 3.29 (dq, $J = 13.0, 3.6$ Hz, 1H), 3.27–3.61 (m, 3H), 3.88–4.16 (m, 4H), 4.56 (br d, $J = 5.6$ Hz, 2H), 4.61 (br s, 1H), 4.73–4.77 (m, 1H), 5.18 (d, $J = 6.8$ Hz, 1H), 5.20 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.29 (dq, $J = 17.3,$

1.4 Hz, 1H), 5.56 (dt, $J = 15.1, 6.8$ Hz, 1H), 5.80 (d, $J = 10.7$ Hz, 1H), 5.92 (ddt, $J = 10.7, 17.3, 5.6$ Hz, 1H), 6.23 (dd, $J = 10.7, 15.1$ Hz, 1H) and 7.20–7.34 (m, 5H, aromatic); δ_{C} (75 MHz; CDCl_3) 12.5, 12.7, 14.2, 15.2, 15.3, 15.4, 15.7, 17.3, 20.0, 20.5, 30.2, 31.3, 32.1, 33.1, 33.9, 37.8, 41.2, 46.9, 50.5, 55.7, 59.6, 60.4, 60.7, 65.4, 65.8, 66.0, 75.3, 98.6, 100.0, 117.6, 121.8, 122.2, 126.2, 126.3, 126.9, 127.3, 128.9, 129.4, 132.1, 133.0, 134.6, 134.7, 135.1, 135.3, 135.4, 152.7, 156.4, 175.1 and 175.4.

(2S,3S,5E,8E,10E,14S)-15-Allyloxycarbonylamino-3-(1-ethoxyethoxy)-2,6,8,14-tetramethylpentadeca-5,8,10-trien-1-ol 25

To an ice-cooled solution of amide **24** (335 mg, 5.24×10^{-1} mmol) in MeOH (0.46 cm^3) and THF (5.5 cm^3) was added dropwise a solution of lithium borohydride (2.80 cm^3 ; 2.0 M solution in THF, 5.6 mmol). After being stirred for 1 h, the reaction mixture was quenched by addition of water. The solvent was removed *in vacuo*, and the resulting slurry was extracted three times with Et_2O . The combined extract was washed with brine, dried (MgSO_4) and concentrated *in vacuo*, and the residue was purified by flash chromatography (hexane– EtOAc , 3 : 1) to give alcohol **25** (90.8 mg, 37%) (R_{f} 0.34 [hexane– EtOAc 2 : 1]) and its diastereomer (90.3 mg, 37%) (R_{f} 0.23 [hexane– EtOAc 2 : 1]) as a colorless oil (Found: C, 69.43; H, 10.29; N, 3.22. Calc. for $\text{C}_{27}\text{H}_{47}\text{NO}_5$: C, 69.64; H, 10.17; N, 3.01%; $[\alpha]_{\text{D}}^{25} -2.2$ (c 0.875, CHCl_3); δ_{H} (300 MHz; CDCl_3) (R_{f} 0.34) 0.82 (d, $J = 7.1$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.27 (d, $J = 5.1$ Hz, 3H), 1.31–1.66 (m, 8H), 1.83 (br s, 1H), 2.04–2.43 (m, 4H), 2.68 (m, 2H), 2.99–3.16 (m, 2H), 3.41–3.59 (m, 5H), 3.83 (dt, $J = 6.9, 2.7$ Hz, 1H), 4.56 (d, $J = 5.6$ Hz, 2H), 4.68 (q, $J = 5.1$ Hz, 1H), 4.76 (br s, 1H), 5.18 (d, $J = 6.8$ Hz, 1H), 5.20 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.29 (dq, $J = 17.3, 1.4$ Hz, 1H), 5.56 (dt, $J = 15.1, 6.8$ Hz, 1H), 5.80 (d, $J = 10.7$ Hz, 1H), 5.93 (ddt, $J = 10.7, 17.3, 5.6$ Hz, 1H) and 6.24 (dd, $J = 10.7, 15.1$ Hz, 1H) and (R_{f} 0.23) 0.89 (d, $J = 7.3$ Hz, 3H), 0.91 (d, $J = 7.3$ Hz, 3H), 1.19 (t, $J = 7.3$ Hz, 3H), 1.32 (d, $J = 5.4$ Hz, 3H), 1.40–1.68 (m, 8H), 1.86–2.38 (m, 4H), 2.68 (s, 2H), 2.99–3.13 (m, 2H), 3.48–3.73 (m, 6H), 4.56 (d, $J = 5.6$ Hz, 2H), 4.72–4.81 (m, 2H), 5.19–5.33 (m, 3H), 5.56 (dt, $J = 15.1, 6.8$ Hz, 1H), 5.79 (d, $J = 10.7$ Hz, 1H), 5.93 (ddt, $J = 10.7, 17.3, 5.6$ Hz, 1H) and 6.24 (dd, $J = 10.7, 15.1$ Hz, 1H); δ_{C} (75 MHz; CDCl_3) (R_{f} 0.34) 9.9, 15.1, 15.8, 16.1, 17.3, 20.2, 30.1, 30.8, 33.1, 33.9, 46.8, 50.4, 61.5, 65.1, 65.4, 76.3, 100.1, 117.5, 122.3, 126.3, 126.8, 133.0, 134.4, 134.8 and 156.4; (R_{f} 0.23) 11.2, 15.2, 15.8, 16.0, 17.3, 20.3, 30.1, 30.2, 33.0, 33.9, 37.5, 46.8, 50.4, 60.4, 65.4, 65.6, 78.2, 99.5, 117.5, 122.6, 126.2, 126.9, 132.2, 133.0, 134.5, 134.8 and 156.4.

(2R,3S,5E,8E,10E,14S)-15-Allyloxycarbonylamino-3-(1-ethoxyethoxy)-2,6,8,14-tetramethylpentadeca-5,8,10-trienal

A solution of alcohol **25** (103 mg, 2.21×10^{-1} mmol) in CH_2Cl_2 (2.5 cm^3) was cooled to 0 °C and Dess–Martin periodinane (154 mg, 3.63×10^{-1} mmol) was added. The reaction mixture was stirred for 30 min at rt. The reaction was quenched by addition of 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was then extracted twice with Et_2O . The combined extract was washed successively with saturated aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexane– EtOAc , 3 : 1) to give title aldehyde as a colorless oil (61.7 mg, 60%); ν_{max} (neat)/ cm^{-1} 3348 (br), 2721, 1728, 1703, 1533 and 1246; δ_{H} (300 MHz; CDCl_3) 0.91 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 7.1$ Hz, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.27 (d, $J = 5.4$ Hz, 3H), 1.40–1.67 (m, 8H), 2.04–2.51 (m, 4H), 2.74 (s, 2H), 2.97–3.17 (m, 2H), 3.36–3.65 (m, 3H), 4.08–4.13 (m, 1H), 4.55 (br d, $J = 5.4$ Hz, 2H), 4.75 (dq, $J = 18.2, 5.4$ Hz, 1H), 4.88 (br s, 1H), 5.15 (t, $J = 6.8$ Hz, 1H), 5.20 (dq, $J = 10.4, 1.4$ Hz, 1H), 5.30 (dq, $J = 17.3, 1.4$ Hz, 1H), 5.56 (dt, $J = 15.1, 6.8$ Hz, 1H), 5.79 (d, $J = 10.7$ Hz, 1H), 5.92 (ddt, $J = 10.7, 17.3, 5.6$ Hz, 1H), 6.23 (dd, $J = 10.7, 15.1$ Hz, 1H) and 9.75 (s, 1H); δ_{C} (75 MHz; CDCl_3) 7.7, 15.1, 15.2, 15.8, 16.0, 17.2, 20.1, 20.2,

30.1, 30.6, 31.5, 33.0, 33.8, 46.8, 49.5, 49.7, 59.7, 60.1, 65.3, 75.0, 75.5, 98.8, 99.7, 117.4, 121.2, 121.4, 126.3, 126.7, 132.3, 133.0, 134.1, 136.3, 156.3, 204.4 and 204.6.

2-Trimethylsilylethyl (2*E*,4*E*,6*S*,7*S*,9*E*,12*E*,14*E*,18*S*)-19-allyloxycarbonylamino-7-(1-ethoxyethoxy)-6,10,12,18-tetramethylnonadeca-2,4,9,12,14-pentaenoate **27**

To a solution of Wittig–Horner reagent **26** (107 mg, 3.32×10^{-1} mmol) in THF (1.5 cm³) was added dropwise lithium hexamethyldisilazide (0.31 cm³; 1.0 M in THF, 3.1×10^{-1} mmol) at -78°C . After stirring of this mixture for 10 min, a solution of the aldehyde (61 mg, 1.3×10^{-1} mmol) in THF (2 cm³) was slowly added. The resulting mixture was warmed to -25°C , and was stirred for an additional 40 min. Water (2 cm³) was added to the reaction mixture to quench the reaction. The solvent was then removed *in vacuo*, and the aqueous layer was extracted three times with Et₂O. The combined extract was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane–EtOAc, 2 : 1) to give ester **27** (80 mg, 96%) as a colorless oil (Found: C, 68.30; H, 9.94; N, 2.12. Calc. for C₃₆H₆₁NO₆Si: C, 68.42; H, 9.73; N, 2.22%). [α]_D²⁸ -24.1 (*c* 0.87, CHCl₃); ν_{max} (neat)/cm⁻¹ 3354 (br), 1730, 1712, 1250, 860 and 837; δ_{H} (300 MHz; CDCl₃) 0.05 (s, 9 H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 8.6 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.15–1.26 (m, 8H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.50 (s, 3H), 1.64 (s, 3H), 2.09–2.23 (m, 2H), 2.68 (s, 2H), 2.97–3.18 (m, 2H), 3.43–3.65 (q and m, *J* = 7.1 Hz, 4H), 4.24 (t, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.75 (q, *J* = 5.1 Hz, 2H), 5.19 (d, *J* = 6.8 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.30 (dq, *J* = 17.3, 1.4 Hz, 1H), 5.56 (dt, *J* = 15.1, 6.8 Hz, 1H), 5.78 (d, *J* = 10.7 Hz, 1H), 5.78 (d, *J* = 14.7 Hz, 1H), 5.92 (ddt, *J* = 10.7, 17.3, 5.6 Hz, 1H), 6.15–6.18 (m, 2H), 6.24 (dd, *J* = 10.7, 15.1 Hz, 1H) and 7.24 (ddt, *J* = 7.8, 14.7, 2.0 Hz, 1H); δ_{C} (75 MHz; CDCl₃) -1.5 , 14.1, 14.4, 15.0, 15.3, 15.8, 16.0, 17.3, 20.2, 20.4, 30.1, 30.3, 31.0, 33.1, 33.4, 40.1, 40.8, 46.8, 50.4, 59.7, 59.8, 60.3, 62.3, 65.3, 79.1, 80.1, 98.8, 99.8, 119.8, 119.9, 121.9, 122.3, 126.2, 126.3, 126.8, 127.9, 128.0, 132.2, 133.0, 134.4, 134.5, 134.9, 135.1, 144.7, 144.8, 146.3, 146.6, 156.3 and 167.3.

(6*S*,7*S*,18*S*)-20-Aza-6,10,12,18-tetramethyl-7-(1-ethoxyethoxy)cycloicosa-2,4,9,12,14-pentaenone (O-EE-aglycone) **28**

To a solution of ester **27** (140.7 mg, 2.23×10^{-1} mmol) and 1,3-dimethylbarbituric acid (228 mg, 1.46 mmol) in THF (15 cm³) was added tetrakis(triphenylphosphine)palladium (43.9 mg, 3.79×10^{-2} mmol, 17 mol%), and the resulting mixture was stirred at rt for 27 h. The mixture was then poured into saturated aq. NaHCO₃ and extracted four times with Et₂O. The combined extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography (CHCl₃–MeOH, 20 : 1 to 2 : 1) to give the corresponding free amino ester as a colorless oil (79.5 mg, 65%) {LRFABMS (NBA matrix) *m/z*, 548.3 [(M + H)⁺; Calc. for C₃₂H₅₈NO₆Si: *m/z* 548.1]; ν_{max} (neat)/cm⁻¹ 2958, 1701, 1215 and 758; δ_{H} (300 MHz; CDCl₃) 0.05 (s, 9 H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.99–1.10 (m, 8H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.50 (s, 3H), 1.64 (s, 3H), 1.90 (br s, 2H), 2.10–2.25 (m, 3H), 2.48–2.74 (m, 4H), 3.46–3.64 (m, 3H), 4.23 (t, *J* = 8.5 Hz, 2H), 4.73 (dq, *J* = 5.3, 15.1 Hz, 1H), 5.58 (dt, *J* = 6.8, 15.1 Hz, 1H), 5.78 (d, *J* = 10.7 Hz, 1H), 5.78 (d, *J* = 10.7 Hz, 1H), 5.79 (d, *J* = 14.7 Hz, 1H), 6.12–6.18 (m, 2H), 6.25 (dd, *J* = 10.7, 15.1 Hz, 1H) and 7.24 (ddt, *J* = 14.7, 7.8, 2.0 Hz, 1H).

To an ice-cooled solution of the amino ester (79.5 mg, 1.45×10^{-1} mmol) in THF (10 cm³) was added TBAF (0.40 cm³ of 1.0 M THF solution, 4.0×10^{-1} mmol). After being stirred at rt for 24 h, the mixture was poured into water and extracted six times with CHCl₃. The combined extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was used for the next step without further purification.

The residue was dissolved in dry DMF (80 cm³) and cooled in an ice–water-bath. To the ice-cooled solution were added dropwise diethyl cyanophosphonate (140 mm³; 93% purity 8.59×10^{-1} mmol) and triethylamine (150 mm³, 1.08 mmol). The reaction mixture was stirred for an additional 3 h at 0°C . The mixture was then poured into water and extracted three times with Et₂O. The combined extract was washed successively with water, saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by PLC (hexane–EtOAc, 2 : 1) to give lactam **28** as a colorless solid (17.6 mg, 28%) {HRFABMS (NBA matrix) *m/z* 430.3366 [(M + H)⁺; Calc. for C₂₇H₄₄NO₃: *m/z*, 430.3321]; [α]_D²⁶ + 65 (*c* 0.563, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 2978, 2929, 1658, 1631, 1604, 1379, 1120, 1095, 1030 and 997; δ_{H} (300 MHz; CDCl₃) 0.95 (d, *J* = 7.1 Hz, 3H), 1.07–1.14 (m, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 5.1 Hz, 3H), 1.50 (s, 3H), 1.71 (s, 3H), 2.07–2.42 (m, 6H), 2.71–2.92 (m, 2H), 3.14–3.32 (m, 2H), 3.40–3.72 (m, 4H), 4.72 (q, *J* = 5.4 Hz, 1H), 4.83 (q, *J* = 5.4 Hz, 1H), 5.14 (dt, *J* = 8.6, 17.3 Hz, 1H), 5.53–5.84 (m, 5H), 6.34 (dd, *J* = 10.7, 15.1 Hz, 1H) and 6.91 (dd, *J* = 11.2, 14.9 Hz, 1H).

(6*S*,7*S*,18*S*)-20-Aza-6,10,12,18-tetramethyl-7-(trimethylsilyloxy)cycloicosa-2,4,9,12,14-pentaenone (O-TMS-aglycone) **2**

To a solution of compound **28** (21.1 mg, 4.91×10^{-2} mmol) in MeOH (10 cm³) was added PPTS (8.0 mg, 3.2×10^{-2} mmol) at rt. The reaction mixture was stirred for 5 h. The mixture was treated with Et₃N (0.30 cm³, 2.15 mmol) and concentrated *in vacuo*. To an ice-cooled mixture of the residue in CH₂Cl₂ (7 cm³) containing DMAP (7.5 mg, 3.0×10^{-2} mmol) and Et₃N (1.00 cm³, 7.17 mmol) was added dropwise TMSCl (0.30 cm³, 2.36 mmol), and the reaction mixture was stirred for 45 min. The reaction was quenched by addition of ice–water and the resulting mixture was extracted twice with Et₂O. The combined extract was washed successively with saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 7 : 1 to 4 : 1) to afford title compound **2** (19.5 mg, 92%);

Methyl 3-O-acetyl-2,4,6-trideoxy-4-[fluoren-9-ylmethoxy-carbonyl(methyl)amino]- α -D-ribo-hexopyranoside **30**

To an ice-cooled solution of compound **29**⁹ (128.5 mg, 3.23×10^{-1} mmol) and DMAP (65 mg, 5.3×10^{-1} mmol) in pyridine (4.0 cm³) was added Ac₂O (0.50 cm³, 5.30 mmol) and the mixture was stirred at rt for 1 h. The reaction was quenched by addition of ice–water at 0°C and the resulting mixture was stirred for several minutes at rt, and extracted twice with Et₂O. The combined extract was washed successively with water, saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 5 : 1 to 2 : 1) to afford acetate **30** as a colorless, amorphous solid (126.3 mg, 89%) {HRFABMS (NBA matrix) *m/z* 440.2112 [(M + H)⁺; Calc. for C₂₅H₃₀NO₆: *m/z*, 440.2073]; mp 95.5–98.0 $^\circ\text{C}$; [α]_D²⁶ + 162 (*c* 0.585, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 1736, 1693, 1321, 1252, 1128 and 1066; δ_{H} (500 MHz; CDCl₃) 1.02 (d, *J* = 6.2 Hz, 3H, H-6), 1.17 (d, *J* = 6.3 Hz, 3H, H-6), 1.57 (ddd, *J* = 3.9, 3.9, 15.2 Hz, 1H, H-2_{ax}), 1.96 (ddd, *J* = 4.1, 4.1, 15.3 Hz, 1H, H-2_{ax}), 2.00 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.07 (dd, *J* = 2.2, 15.2 Hz, 1H, H-2_{eq}), 2.19 (dd, *J* = 2.3, 15.3 Hz, 1H, H-2_{eq}), 2.78 (s, 3H, NMe), 2.80 (s, 3H, NMe), 3.30 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.39 (dd, *J* = 2.7, 10.1 Hz, 1H, H-4), 4.03 (br s, 1H, H-4), 4.17–4.24 (m, 1H, H-5), 4.21–4.27 (m, 2H, Fmoc CH₂), 4.33 (br s, 1H, H-5), 4.47 (d, *J* = 6.7 Hz, 2H, Fmoc CH₂), 4.48–4.53 (m, 1H, Fmoc CH), 4.59 (d, *J* = 4.2 Hz, 1H, H-1), 4.61–4.67 (m, 2H, H-3 and Fmoc CH), 4.67 (d, *J* = 4.2 Hz, 1H, H-1), 5.08 (ddd, *J* = 2.2, 2.3, 4.1 Hz, 1H, H-3), 7.28–7.35 (m, 4H, Fmoc Ar), 7.36–7.42 (m, 4H, Fmoc Ar), 7.51–7.60 (m, 4H, Fmoc Ar) and 7.73–7.77 (m, 4H, Fmoc Ar); δ_{C} (126 MHz; CDCl₃) 18.2, 18.3, 21.4, 21.5, 31.1, 33.3, 33.5, 47.26, 47.32, 55.2, 57.7, 60.4, 60.6, 66.9, 67.3, 70.3,

97.1, 97.3, 119.8, 119.9, 124.5, 124.6, 124.8, 124.9, 126.96, 126.98, 127.0, 127.1, 127.6, 141.25, 141.27, 141.3, 143.8, 143.9, 156.1, 156.6, 170.16 and 170.25.

1,3-Di-*O*-acetyl-2,4,6-trideoxy-4-[fluoren-9-ylmethoxycarbonyl(methyl)amino]- α -D-ribo-hexopyranose **31**

A solution of glycoside **30** (122.5 mg, 2.79×10^{-1} mmol) in AcOH (8.2 cm³) and water (1.7 cm³) was heated at around 95 °C for 2.5 h. The reaction mixture was evaporated *in vacuo* with an aid of azeotropic distillation with toluene. To a solution of the obtained crude hemiacetal and DMAP (3.2 mg, 2.6×10^{-2} mmol) in pyridine (2.0 cm³) was added Ac₂O (0.25 mm³, 2.65 mmol) and the mixture was stirred at rt for 1 h. The reaction was quenched by addition of ice-water at 0 °C and the resulting mixture was stirred for several minutes at rt, and extracted twice with Et₂O. The combined extract was washed successively with water, saturated aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc, 5 : 1 to 2 : 1) to afford diacetate **31** as a colorless powder (125.9 mg, 97%) {HRFABMS (NBA matrix) *m/z* 468.2026 [(M + H)⁺; Calc. for C₂₆H₃₀NO₇: *m/z*, 468.2022]}; mp 50.0–55.0 °C; [α]_D²⁶ +79 (c 0.530, CHCl₃); ν_{\max} (CHCl₃)/cm^{−1} 1743, 1697, 1317, 1240 and 1066; δ_{H} (500 MHz; CDCl₃) 0.96 (d, *J* = 6.2 Hz, 3H, H-6), 1.06 (br d, *J* = 5.2 Hz, 3H, H-6), 1.16 (d, *J* = 6.2 Hz, 3H, H-6), 1.20 (d, *J* = 6.1 Hz, 3H, H-6), 1.55 (ddd, *J* = 3.0, 10.6, 13.8 Hz, 1H, H-2_{ax}), 1.55–1.61 (m, 1H, H-2), 1.91–1.98 (m, 1H, H-2), 1.93–1.98 (m, 1H, H-2), 2.01 (s, 3H, Ac), 2.04 (s, 6H, Ac), 2.076 (s, 3H, Ac), 2.078 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.03–2.12 (m, 2H, H-2 × 2), 2.07–2.13 (m, 1H, H-2), 2.22–2.27 (m, 1H, H-2), 2.73 (s, 3H, NMe × 2), 2.76 (s, 3H, NMe), 2.78 (s, 3H, NMe), 3.28 (dd, *J* = 2.5, 10.3 Hz, 1H, H-4), 3.35 (br d, *J* = 8.8 Hz, 1H, H-4), 4.01 (br s, 1H, H-4), 4.12 (br s, 2H, H-4 and H-5), 4.21–4.28 (m, 3H, Fmoc CH × 2 and H-5), 4.21–4.30 (m, 3H, Fmoc CHH × 2 and H-5), 4.40–4.47 (m, 1H, H-5), 4.46–4.52 (m, 4H, Fmoc CH × 2 and Fmoc CHH × 2), 4.52–4.59 (m, 1H, Fmoc CHH), 4.54–4.60 (m, 1H, Fmoc CHH), 4.55–4.60 (m, 1H, H-3), 4.65 (dd, *J* = 5.1, 10.7 Hz, 1H, Fmoc CHH), 4.70 (dd, *J* = 4.7, 10.7 Hz, 1H, Fmoc CHH), 4.82 (br s, 1H, H-3), 5.14 (br q, *J* = 2.2 Hz, 1H, H-3), 5.34 (br q, *J* = 2.8 Hz, 1H, H-3), 5.82 (br d, *J* = 10.0 Hz, 1H, H-1), 5.94 (dd, *J* = 2.1, 10.2 Hz, 1H, H-1), 6.00 (d, *J* = 4.0 Hz, 1H, H-1), 6.10 (d, *J* = 4.0 Hz, 1H, H-1), 7.29–7.36 (m, 8H, Fmoc Ar), 7.37–7.43 (m, 8H, Fmoc Ar), 7.51–7.59 (m, 8H, Fmoc Ar) and 7.74–7.79 (m, 8H, Fmoc Ar); δ_{C} (126 MHz; CDCl₃) 18.2, 18.4, 18.5, 21.02, 21.03, 21.06, 21.1, 21.2, 21.3, 30.8, 30.9, 32.4, 32.7, 34.9, 35.1, 47.26, 47.33, 47.4, 57.3, 57.7, 63.1, 63.3, 66.8, 67.1, 67.4, 68.6, 68.7, 69.8, 70.9, 71.1, 90.0, 90.2, 90.3, 90.4, 119.88, 119.90, 119.93, 119.95, 120.0, 124.36, 124.42, 124.45, 124.52, 124.81, 124.83, 127.00, 127.02, 127.08, 127.10, 127.2, 127.5, 127.65, 127.67, 127.73, 141.3, 141.4, 143.78, 143.81, 143.88, 143.90, 155.9, 156.0, 156.6, 169.17, 169.19, 169.3, 169.4, 169.56, 169.61 and 169.7.

Vicenistatin [(6*S*,7*S*,18*S*)-20-aza-6,10,12,18-tetramethyl-7-*O*-(2',4',6'-trideoxy-4'-methylamino- β -D-ribo-hexopyranosylcyclo-icoso-2,4,9,12,14-pentaenone) **1**

To a suspension of AgClO₄ (7.0 mg, 3.4×10^{-2} mmol) in dry CH₂Cl₂ (5 cm³) was added dropwise SnCl₄ (35 mm³; 1 M in CH₂Cl₂, 3.5×10^{-2} mmol) at rt. The mixture was shielded from light and stirred for 1 h. To the ice-cooled mixture was added dropwise a solution of **31** (46.4 mg, 9.92×10^{-2} mmol) and **2** (19.5 mg, 4.53×10^{-2} mmol) in dry CH₂Cl₂ (2.4 cm³), and the whole was stirred for 1 h. The mixture was treated with saturated aq. NaHCO₃ and extracted twice with Et₂O. The combined extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by PLC (hexane–EtOAc, 1 : 1) to afford 3'-*O*-acetyl-4'-*N*-Fmoc-vicenistatin (20.6 mg, 59%; mixture of α - and β -anomer), which was used for the next step without further purification.

To a solution of 3'-*O*-acetyl-4'-*N*-Fmoc-vicenistatin (12.3 mg, 1.60×10^{-2} mmol) in EtOAc (5 cm³) was added DBU (20 mm³, 1.3×10^{-1} mmol), and the mixture was stirred for 0.5 h at rt. The mixture was diluted with EtOAc and washed with saturated aq. NaHCO₃. The aqueous washings were extracted twice with EtOAc. The combined extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by PLC (benzene–acetone, 25 : 4) to afford 3'-*O*-acetyl-vicenistatin **32** (4.0 mg, 46%) and its α -anomer (4.0 mg, 46%); δ_{H} (500 MHz; CDCl₃) 0.95 (d, *J* = 6.9 Hz, 3H, H-23), 1.05 (d, *J* = 6.6 Hz, 3H, H-20), 1.32 (d, *J* = 6.2 Hz, 3H, H-6'), 1.41–1.47 (m, 2H, H-17), 1.54 (s, 3H, H-21), 1.65–1.75 (m, 1H, H-18), 1.74 (ddd, *J* = 2.9, 9.9, 14.2 Hz, 1H, H-2'), 1.77 (s, 3H, H-22), 2.01–2.10 (m, 1H, H-16), 2.12 (s, 3H, Ac), 2.14 (ddd, *J* = 2.1, 3.3, 14.2 Hz, 1H, H-2'), 2.21–2.28 (m, 2H, H-8 and H-16), 2.28 (dd, *J* = 3.0, 9.7 Hz, 1H, H-4'), 2.32–2.38 (m, 1H, H-6), 2.39 (s, 3H, NMe), 2.58 (d, *J* = 14.7 Hz, 1H, H-11), 2.66 (d, *J* = 14.7 Hz, 1H, H-11), 2.60–2.70 (m, 1H, H-8), 3.10 (ddd, *J* = 4.2, 8.3, 13.6 Hz, 1H, H-19), 3.26 (ddd, *J* = 1.6, 7.8, 9.3 Hz, 1H, H-7), 3.39 (ddd, *J* = 7.6, 9.8, 13.6 Hz, 1H, H-19), 3.65 (dq, *J* = 6.2, 9.7 Hz, 1H, H-5'), 4.74 (dd, *J* = 1.8, 9.8 Hz, 1H, H-1'), 5.09 (dd, *J* = 7.1, 7.1 Hz, 1H, H-9), 5.42 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H, H-3'), 5.56 (ddd, *J* = 7.3, 7.3, 14.7 Hz, 1H, H-15), 5.62 (dd, *J* = 4.3, 7.1 Hz, 1H, NH-19), 5.69 (d, *J* = 15.2 Hz, 1H, H-2), 5.74 (d, *J* = 11.0 Hz, 1H, H-13), 5.75 (dd, *J* = 9.5, 15.2 Hz, 1H, H-5), 6.05 (dd, *J* = 10.9, 15.2 Hz, 1H, H-4), 6.33 (dd, *J* = 11.0, 15.1 Hz, 1H, H-14) and 6.95 (dd, *J* = 10.9, 15.1 Hz, 1H, H-3); δ_{C} (126 MHz; CDCl₃) 17.16, 17.19, 18.4, 18.7, 19.1, 21.1, 28.5, 33.3, 33.6, 34.0, 35.2, 36.2, 43.7, 45.0, 49.3, 62.8, 67.5, 70.9, 85.4, 99.7, 121.9, 123.8, 126.2, 128.0, 128.3, 132.5, 134.3, 134.7, 139.4, 142.5, 166.0 and 170.3.

To a solution of acetate **32** (4.3 mg, 7.9×10^{-3} mmol) in MeOH (5 cm³) was added 5.0 M KOH (3.0 cm³, 15 mmol) and the mixture was stirred at rt for 3 days. The reaction mixture was evaporated, and the residue was dissolved in a minimum amount of water and extracted three times with EtOAc. The combined extract was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by PLC (CHCl₃–MeOH, 3 : 1) to afford vicenistatin **1** (3.3 mg, 83%); {HRFABMS (NBA matrix) *m/z* 501.3698 [(M + H)⁺; Calc. for C₃₀H₄₉N₂O₄: *m/z*, 501.3692]}; δ_{H} (500 MHz; pyridine-*d*₅) 0.84 (d, *J* = 6.9 Hz, 3H, H-23), 1.08 (d, *J* = 6.6 Hz, 3H, H-20), 1.42–1.50 (m, 1H, H-17), 1.51–1.63 (m, 1H, H-17), 1.52 (d, *J* = 6.2 Hz, 3H, H-6'), 1.70 (s, 3H, H-21), 1.80–1.88 (m, 1H, H-18), 1.91 (ddd, *J* = 3.0, 10.1, 13.1 Hz, 1H, H-2'_{ax}), 1.95 (s, 3H, H-22), 2.02–2.10 (m, 1H, H-16), 2.24 (dd, *J* = 2.9, 9.6 Hz, 1H, H-4'), 2.27 (ddd, *J* = 8.4, 8.4, 13.9 Hz, 1H, H-8), 2.33–2.43 (m, 1H, H-16), 2.37–2.45 (m, 1H, H-6), 2.41 (s, 3H, NMe), 2.38–2.48 (m, 1H, H-2'_{eq}), 2.62 (d, *J* = 15.1 Hz, 1H, H-11), 2.74 (d, *J* = 15.1 Hz, 1H, H-11), 3.03 (ddd, *J* = 2.8, 4.7, 13.4 Hz, 1H, H-19), 3.09 (dd, *J* = 8.3, 13.8 Hz, 1H, H-8), 3.37 (dd, *J* = 8.8, 8.8 Hz, 1H, H-7), 4.01 (dq, *J* = 6.2, 9.7 Hz, 1H, H-5'), 3.98–4.07 (m, 1H, H-19), 4.39 (ddd, *J* = 2.9, 2.9, 2.9 Hz, 1H, H-3'), 5.20 (dd, *J* = 7.5, 7.5 Hz, 1H, H-9), 5.30 (dd, *J* = 1.7, 9.6 Hz, 1H, H-1'), 5.69 (ddd, *J* = 5.2, 9.3, 14.7 Hz, 1H, H-15), 5.86 (dd, *J* = 9.6, 15.1 Hz, 1H, H-5), 5.96 (d, *J* = 11.0 Hz, 1H, H-13), 6.21 (dd, *J* = 11.3, 15.2 Hz, 1H, H-4), 6.26 (d, *J* = 15.0 Hz, 1H, H-2), 6.80 (dd, *J* = 11.1, 14.9 Hz, 1H, H-14), 7.60 (dd, *J* = 11.2, 15.0 Hz, 1H, H-3), 8.49 (dd, *J* = 2.1, 9.2 Hz, 1H, NH); δ_{C} (126 MHz; pyridine-*d*₅) 17.3, 17.7, 17.9, 18.7, 19.5, 27.7, 32.7, 33.5, 34.0, 36.6, 39.4, 43.1, 46.3, 49.3, 63.2, 65.2, 70.5, 86.0, 100.8, 122.0, 124.6, 128.0, 128.4, 128.4, 132.6, 134.0, 135.1, 140.3, 143.3 and 166.3.

Acknowledgements

We thank Dr K. Shindo of Kirin Brewery Co. Ltd. for kindly supplying natural vicenistatin. (*S*)-Citronellal was kindly provided by Takasago International Co. Ltd. This work was supported partly by the 'Research for the Future' Programme of

The Japan Society for the Promotion of Science (JSPS-RFTF96I 00302) and partly by a Grant-in-Aid for Scientific Research (11760089 and 13480185) from the Ministry of Education, Science, Sports and Culture.

References

- 1 K. Shindo, M. Kamishohara, A. Odagawa, M. Matsuoka and H. Kawai, *J. Antibiot.*, 1993, **46**, 1076.
- 2 H. Arai, Y. Matsushima, T. Eguchi and K. Kakinuma, *Tetrahedron Lett.*, 1998, **39**, 3181.
- 3 S. Omura, A. Nakagawa, K. Shibata and H. Sano, *Tetrahedron Lett.*, 1982, **23**, 4713.
- 4 I. Umezawa, H. Takeshima, K. Komiyama, Y. Koh, H. Yamamoto and M. Kawaguchi, *J. Antibiot.*, 1981, **34**, 259.
- 5 K. Kojiri, S. Nakajima, H. Suzuki, H. Kondo and H. Suda, *J. Antibiot.*, 1992, **45**, 868.
- 6 I. Takahashi, Y. Oda, Y. Nishiie, K. Ochiai and T. Mizukami, *J. Antibiot.*, 1997, **50**, 186.
- 7 Y. Matsushima, T. Nakayama, M. Fujita, R. Bhandari, T. Eguchi, K. Shindo and K. Kakinuma, *J. Antibiot.*, 2001, **54**, 211.
- 8 Y. Matsushima, H. Itoh, T. Eguchi and K. Kakinuma, *J. Antibiot.*, 1998, **51**, 688.
- 9 Y. Matsushima, T. Nakayama, S. Tohyama, T. Eguchi and K. Kakinuma, *J. Chem. Soc., Perkin Trans. 1*, 2001, 569.
- 10 K. Toshima and K. Tatsuta, *Chem. Rev.*, 1993, **93**, 1503; T. Mukaiyama, T. Takashima, M. Katsurada and H. Aizawa, *Chem. Lett.*, 1991, 533.
- 11 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127; J. R. Gage and D. A. Evans, *Org. Synth.*, 1993, **Coll. Vol. VIII**, 339.
- 12 N. Miyaoura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, 3437; N. Miyaoura, K. Yamada, H. Sugimoto and A. Suzuki, *Tetrahedron Lett.*, 1981, **22**, 127; N. Miyaoura, K. Yamada, H. Sugimoto and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972.
- 13 M. Julia, S. Julia and R. Guégan, *Bull. Soc. Chim. Fr.*, 1960, 1072.
- 14 W. H. Kruizinga, B. Strutveen and R. M. Kellogg, *J. Org. Chem.*, 1981, **46**, 4321.
- 15 K. Mori, M. Tominaga, T. Takigawa and M. Matsui, *Synthesis*, 1973, 790.
- 16 E. Negishi, D. E. Van Horn, O. King and N. Okukado, *Synthesis*, 1979, 501; E. Negishi, L. F. Valente and M. Kobayashi, *J. Am. Chem. Soc.*, 1980, **102**, 3298; E. Negishi and H. Matsushita, *Org. Synth.*, 1990, **Coll. Vol. VII**, 245.
- 17 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.
- 18 S. Müller, B. Liepold, G. J. Roth and H. J. Bestmann, *Synlett.*, 1996, 521; S. Ohira, *Synth. Commun.*, 1989, **19**, 561.
- 19 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
- 20 B. S. Bal, W. E. Childers Jr. and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091; G. A. Kraus and M. J. Taschner, *J. Org. Chem.*, 1980, **45**, 1176; G. A. Kraus and B. Roth, *J. Org. Chem.*, 1980, **45**, 4825.
- 21 T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
- 22 K. C. Nicolaou, S. P. Seitz, M. R. Pavia and N. A. Petasis, *J. Org. Chem.*, 1979, **44**, 4011.
- 23 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155; D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277; R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.
- 24 H. Kunz and C. Unverzagt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 436.
- 25 S. F. Martin and C. L. Campbell, *J. Org. Chem.*, 1988, **53**, 3184.
- 26 H. Kunz and J. März, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1375.
- 27 S. Yamada, Y. Kasai and T. Shioiri, *Tetrahedron Lett.*, 1973, 1595.
- 28 U. Schmidt, K. Mundinger, R. Mangold and A. Lieberknecht, *J. Chem. Soc., Chem. Commun.*, 1990, 1216.